VOLUME 59 • JANUARY 1958 • NUMBER 1

OPHTHALMOLOGY

The National Committee for Research in Ophthalmology and Blindness
Frank W. Newell

Stereoscopic Vision and the Duration of the Stimulus
Kenneth N. Ogle and Marianne P. Weil

Spiral Visual Fields
T. F. Schlaegel Jr.

Diverging Exercises While Accommodating
Conrad Berens, Vivian Brackett, and B. Evelyn Taylor

Chiasmal Optic Neuritis
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Studies on the Structure of the Vitreous Body
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A Study of the Relationship Between Adenovirus and Epidemic Keratoconjunctivitis
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Jules François

Lids, Lacrimal Apparatus, and Conjunctiva
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Encephaloma of the Eye
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Ocular Manifestations of Riley-Day Syndrome: Familial Autonomic Dysfunction
Metric System
Victor C. Rambo

Retinitis Pigmentosa with Normal Electroretinogram
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Mydriatic Treatment of Shallow Chamber After Cataract Extraction
Alfredo Villaseca Kenneth C. Swan

Histopathology of the Star-Figure of the Macular Area in Diabetic and Angiospastic Retinopathy
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TABLE OF CONTENTS

VOLUME 59 JANUARY 1958 NUMBER 1

EDITORIALS

PAGE

The National Committee for Research in Ophthalmology and Blindness
Frank W. Newell, M.D., Evanston, Ill. 1

ORIGINAL ARTICLES

Stereoscopic Vision and the Duration of the Stimulus
Kenneth N. Ogle, Ph.D., and Marianne P. Weil, M.A., Rochester, Minn. 4

Spiral Visual Fields
T. F. Schlaegel Jr., M.D., Indianapolis 18

Diverging Exercises While Accommodating
Conrad Berens, M.D.; Vivian Brackett, R.N., and B. Evelyn Taylor, New York .. 24

Chiasmal Optic Neuritis
Roberto Buxeda, M.D., San Juan, P. R. 29

Studies on the Structure of the Vitreous Body
J. A. Szirmai, M.D., and E. A. Balazs, M.D., Boston 34

A Study of the Relationship Between Adenovirus and Epidemic Keratoconjunctivitis
Chie Tanaka, M.D., Bethesda, Md. 49

Morphological Study on Alloxan-Induced Cataract
Ludwig von Sallmann, M.D.; Leo Caravaggio, M.S.; Patricia Grimes, B.A., and Eleanor M. Collins, Bethesda, Md. 55

Treatment of Experimental Herpes Simplex Iridocyclitis with Human Serum Gamma-Globulin
Jed Lee Howard, A.B., and Henry F. Allen, M.D., Boston 68

Thermal Detachment of the Anterior Lamella of the Anterior Lens Capsule
Alston Callahan, M.D., Birmingham, Ala., and Bertha A. Klien, M.D., Chicago 73

Comparative Studies on Anesthetic Properties of Primacaine HCl
Harold G. Scheie, M.D., and Neil S. Williams, M.D., Philadelphia 81

The Differential Diagnosis of Tapetoretinal Degenerations
Jules François, M.D., Ghent, Belgium 88

ANNUAL REVIEWS

Lids, Lacrimal Apparatus, and Conjunctiva
Crowell Beard, M.D., San Jose, Calif. 121

CORRESPONDENCE

Encephaloma of the Eye
Julian F. Chisholm Jr., M.D., Boston 145

Symbols for Expressing Intraocular Dynamics
Stewart Duke-Elder and David M. Maurice, London 146

Ocular Manifestations of Riley-Day Syndrome: Familial Autonomic Dysfunction 147

Metric System
Victor C. Rambo, M.D., Mungeli, India 148

Retinitis Pigmentosa with Normal Electroretinogram
Hermann M. Burian, M.D., Iowa City 149
R. A. Skeehan Jr., M.D.; J. W. Passmore, M.D., and John C. Armington, Ph.D., Washington, D. C. 149

Mydriatic Treatment of Shallow Chamber After Cataract Extraction
Alfredo Villaseca, M.D., Santiago, Chile 150
Kenneth C. Swan, M.D., Portland, Ore. 151

Histopathology of the Star-Figure of the Macular Area in Diabetic and Angiospastic Retinopathy
Hector M. Nano, Buenos Aires, Argentina 152
J. Reimer Wolter, M.D., Ann Arbor, Michigan 152

OBITUARIES

Arthur M. Yudkin, M.D. 154

REGULAR DEPARTMENTS

News and Comment 144, 153, 157

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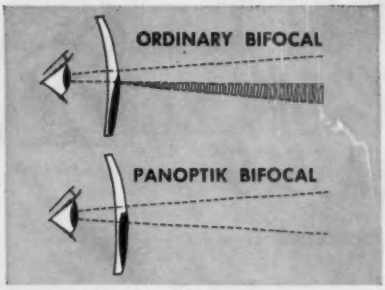

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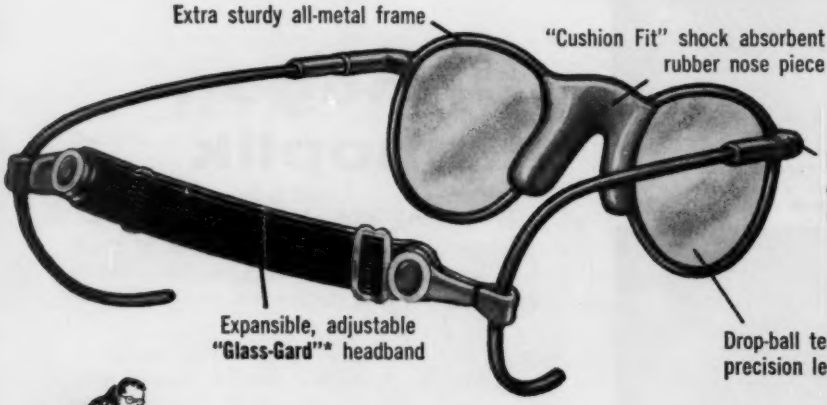
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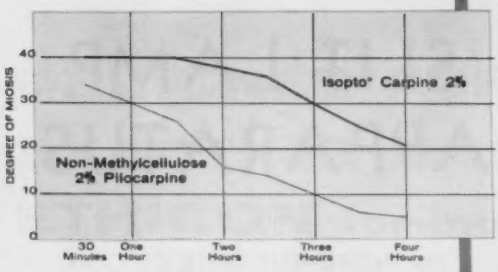

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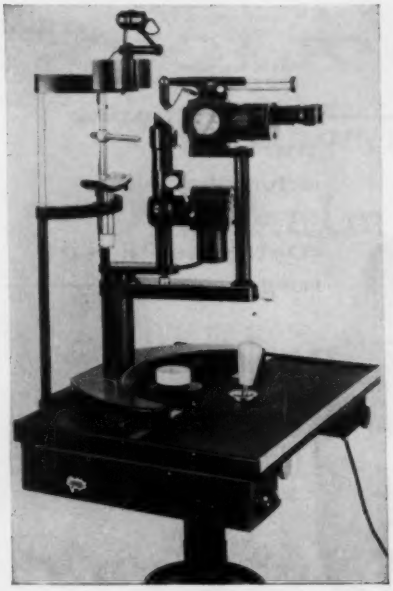

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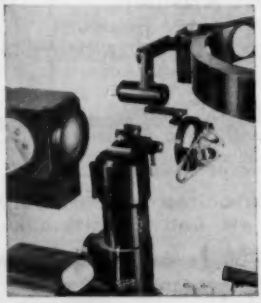

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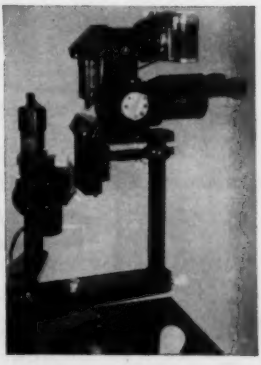

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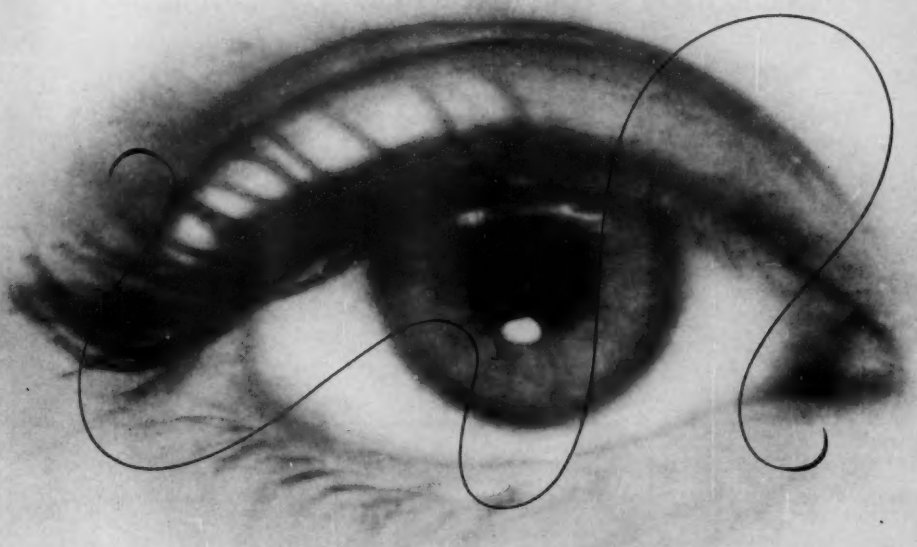

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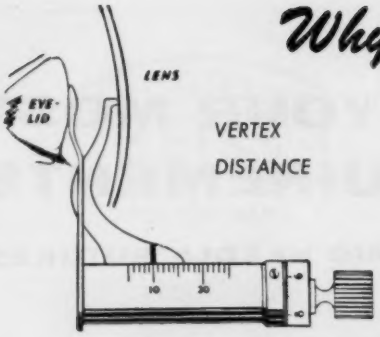

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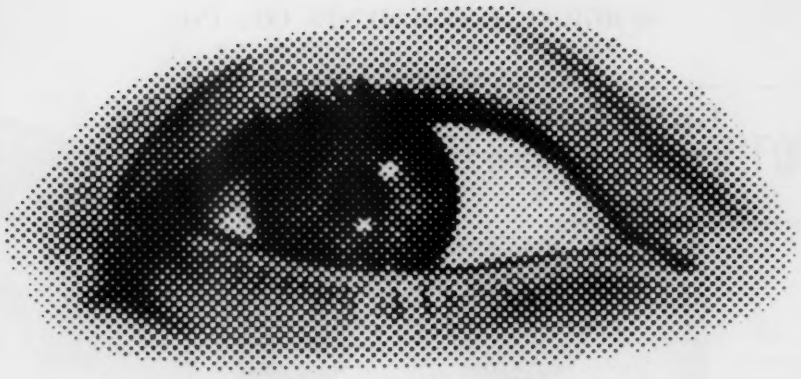

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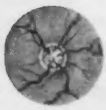

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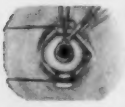

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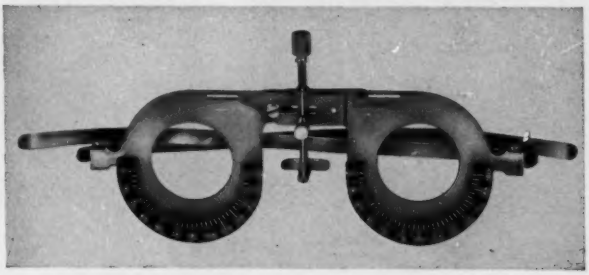

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OPHTHALMOLOGY

Editorials

THE NATIONAL COMMITTEE FOR RESEARCH IN OPHTHALMOLOGY AND BLINDNESS

Organization of the National Committee for Research in Ophthalmology and Blindness was prompted by the four national ophthalmic organizations—the Section on Ophthalmology of the American Medical Association, the American Ophthalmological Society, the Association for Research in Ophthalmology, and the American Academy of Ophthalmology and Otolaryngology. The establishment of such a committee seemed desirable because of the increased funds available for research, the greater number of physicians and scientists devoting full time to research in this field, and the interest of certain lay organizations in transferring their major efforts to blinding disease.

In addition, it was recognized that there was a dearth of qualified ophthalmic scientists, both in the clinical and in the fundamental fields, and that public interest in blinding disease did not parallel the extreme needs in the area. It was further recognized that much research was required in the field of sensory devices and educational methods to benefit those already blinded. It, therefore, appeared wise for representatives of organized ophthalmology to take the initiative in forming a group to stimulate research and to describe the accomplishments as well as the problems presented in the study of blinding diseases and blindness.

The National Committee for Research in Ophthalmology and Blindness has been organized on an informal basis without a complicated administrative structure. An unpaid Secretary-Treasurer is the only officer, and he is responsible for transmitting the activities of the committee to interested persons. It has never been the purpose of the committee to establish a new medical or educational agency or to organize a major central office. Clerical expenses have been met by money appropriated by the ophthalmic organizations which prompted formation of the committee.

In keeping with its simple administrative structure, the National Committee for Research in Ophthalmology and Blindness does not propose to solicit funds or to interfere with the activities of any organization in the field of public relations, service, education, or research. The committee moreover recognizes clearly that these important functions must continue and must be much expanded and that any attempt on its part to channel funds from these functions into laboratory, clinical, or medical studies would be a disservice to ophthalmology, the public, the patients with blinding disease, and the blinded.

Meetings of the National Committee for Research in Ophthalmology and Blindness have been held on June 4, 1957, at the Waldorf-Astoria Hotel in New

York, and Oct. 15, 1957, at the Palmer House in Chicago. The following organizations, each of which has an interest in this field, were represented:

Alfred P. Sloan Foundation, Inc.
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National Council to Combat Blindness, Inc.
National Foundation for Eye Research
National Industries for the Blind
National Institute of Neurological Diseases and Blindness
National Science Foundation
National Society for Prevention of Blindness
Ophthalmological Foundation
Seeing Eye, Inc.
American Academy of Ophthalmology and Otolaryngology
Section on Ophthalmology, American Medical Association
American Ophthalmological Society
Asia-Pacific Academy of Ophthalmology
Association for Research in Ophthalmology

Other national groups with similar interests are welcome to join the committee, and failure to be represented at these meetings may only indicate that difficulty was encountered in contacting them. However, those organizations represented are in agreement with the general aims of the committee and are doing what is possible to cooperate with its purposes.

Because the committee is a loose federation of workers interested in many different aspects of and a variety of methods in approach to the problems of ophthalmic research and blindness, it is believed that it should function as a forum where these groups can express their views. While each group participates in the work of the committee, none can be described as being a member of the committee or as having the committee represent it in any effort.

It is hoped that the National Committee for Research in Ophthalmology and Blindness can serve to integrate the present efforts in promoting research into blinding diseases and blindness. The committee is prepared to provide consultation concerning research to any individual or group requesting such advice. It is felt that those already working in this area have competent medical and lay direction and that it would be presumptuous for this committee to suggest changes in their current activities. However, newcomers to the field may wish to learn in what areas research is being done, what subjects are worthy of attention, and how they can best localize their resources to be most effective.

The following committee projects are now under way:

1. Preparation of a list of the sources of funds and assistance available for research in ophthalmology and blindness, with wide distribution of this list. It is anticipated that this will be completed by Dec. 31, 1957 and will be published in the *American Journal of Ophthalmology* and the A. M. A. ARCHIVES OF OPHTHALMOLOGY and that there will be wide distribution of reprints.

2. Provision of a central directory service and listing of research projects already existing in the field to indicate what studies are already under way and perhaps to prevent duplication.

3. The encouragement of the establishment of training centers for ophthalmic scientists and ophthalmic research laboratory technicians.

4. Active encouragement of research in the field of ophthalmology and blinding diseases by the departments of medicine, pediatrics, obstetrics and gynecology, psychology, and the like in various medical centers.

5. Advisory assistance to those interested in ophthalmic research, particularly stimulation of research in areas where study is needed, with assistance in seeking financial aid and technical personnel.

FRANK W. NEWELL, M.D., Secretary-Treasurer
The National Committee for Research in
Ophthalmology and Blindness
Committee office: 406-C South Blvd.,
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Stereoscopic Vision and the Duration of the Stimulus

KENNETH N. OGLE, Ph.D., and MARIANNE P. WEIL, M.A., Rochester, Minn.

Introduction

Dove (1841)* showed that stereoscopic depth could be perceived when drawings viewed in a stereoscope were illuminated by a flash of very short duration from an electric spark. The results of this experiment, and of the many others based on it subsequently, have been cited as evidence that neither convergence movements of the eyes nor proprioceptive influences from the external muscles of the eyes are necessary for a stereoscopic perception of depth. Hering's[2] falling-bead test, in which the bead would be in view between 1/20 and 1/50 second, and other studies such as those of Smith,[3] provided similar evidence.

Karpinska[4] sought to show that these experiments succeeded, however, only when the observer knew beforehand for what he was looking. Skubich[5] extended Karpinska's introspective experiments to include real objects and found that the depth distance between two objects such as beads could be recognized distinctly with short exposures without a distinct perception of the object configurations themselves. He concluded that binocular discrimination of the distances between separate objects in space might differ from the perception of corporeal configurations, especially those which might be encountered in the drawings used in a stereoscope. Furthermore, he concluded that any increase or reduction of exposure time had little influence on the specific form of interpretation of depth by individual subjects.

Received for publication April 11, 1957.

Mayo Clinic and Mayo Foundation; Section of Biophysics and Biophysical Research (Dr. Ogle). The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

* Cited in Reference 1.

Langlands[6] seems to have been the first to determine quantitatively the influence of the duration of the stimulus on stereoscopic acuity. He used a modification of the three-rod test for stereopsis, the rods being seen silhouetted against a background that could be momentarily illuminated. Although the results of his early work are difficult to summarize, they showed little consistent variation in stereoscopic thresholds with duration of stimulus. His later experiments[7] showed, though, that for exposures longer than 3 to 4 seconds there was a constant low threshold of stereoscopic depth, for exposures from 3 seconds to 1/10 second there was a rapid increase in stereoscopic threshold, but for exposures shorter than 1/10 second the threshold again leveled off to a constant value. Curves illustrating these results are frequently reproduced in the literature. Later experiments by Geblewicz and Shen,[8] who used a stereoscope in total darkness and exposures from 4 to 20 milliseconds, showed that exposure times had little or no apparent influence on depth perception.

Using Monjé's principle of the "stereoeidometer," Hertel and Monjé[9] investigated the influence of exposure time on stereoscopic thresholds in the range 40 to 500 milliseconds. They found a regular increase in threshold with reduction of exposure time. The Monjé test,[10] again, consists of the usual three-rod apparatus, but the three rods are mounted in a large ring that can be turned about an axis in the sagittal line of the observer. In the test the central rod is displaced a certain amount from the plane of the two lateral rods, and then the whole apparatus is slowly turned from the position where the rods are horizontal to some angle at which the subject first perceives

the displacement of the central rod. The stereoscopic threshold is then recorded in terms of the angle through which the direction of these three rods has been turned. A difference in results was found, depending on whether the stereoscopic threshold was measured for given exposure times or whether the time threshold was measured for given disparities. For a given angle and a given displacement of the central rod from the two lateral rods, Hertel and Monjé defined a "principal effective time" (*Hauptnutzzeit*) as the shortest time of presentation which still permits the subject to perceive a given difference in depth. However, the Monjé device introduces an unnecessary complication into the determination of stereoacuity. This acuity must rest on transverse (horizontal) disparities between the images in the two eyes. With this apparatus the vertical extent or the vertical component of the inclined rods on which these disparities depend will vary with the inclination of the rods. Also, the particular retinal areas involved will vary with the angle at which the rods are placed. From the point of view of studying stereoscopic acuity with duration of exposure, the procedure of Hertel and Monjé is faulty also, because no specific fixation point was used and the light-adaptation level of the eyes was indeterminate at the moment of observation.

Wagner [11] used a fixed rod and an adjustable rod in the median plane, one above the other. He modified the definition of "principal effective time" to mean the minimal time required for the subject to obtain the same stereoscopic depth impression that he obtained with unlimited exposure. This effective time is longer than that found by Hertel and Monjé, being of the order of $^2/_{10}$ second. For an increase of the depth displacement between the upper and lower rods, the "principal effective time" markedly decreased. Vilmar [12] employed the same type of test to determine "principal effective times" for the retinal periphery.

A study of this literature fails to give us a definitive relationship between exposure time and stereoscopic acuity. Light adaptation, luminance of test object against the background, the fixation point of the eyes, and the retinal portions used during the test are not adequately controlled. Since the relationship is an important one in our understanding of the physiologic processes underlying stereoscopic depth perception, the experimental work described in this paper was undertaken.

In these experiments the following features are emphasized:

1. The eyes were light-adapted to a constant photopic luminance by light from a uniform background and surround.

2. Only the test object for determining stereoscopic depth was subject to varied exposures.

3. The eyes fixated a vertical plumb line seen silhouetted against the bright background. Differences in apparent luminosities of the test line and of the fixation line could not enter as a factor in the judgment of depth. This fixation plumb line could, however, also be illuminated, if desired, to be brighter than the background and comparable to the luminance of the test line.

4. The stimulus to accommodation and to convergence was held constant by a fixation point at 50 cm. from the eyes.

5. The luminance of the test object as seen against the background could be varied to change the contrast.

6. The test line maintained the same luminance, the same size, and the same sharpness of focus for all disparities and all stereoscopic depths. No empirical factors could be operative.

7. The test line was maintained at ½ arc degree to the right of the fixation line, so that the same retinal regions would be used throughout the tests.

8. A second plumb line, ½ arc degree to the left of the fixation line, was used as a reference line. This line could be placed nearer or farther than the fixation line, and then the test line would be judged "nearer"

or "farther" with respect to this reference line. Thus the influence of exposure times on disparate images judged in depth could be obtained.

9. The vertical extent of the fixation, reference, and test lines remained constant.

10. The speeds of the photographic shutter used to regulate the exposure times were carefully determined and checked. Speeds from 1 second to 1/133 second (7.5 milliseconds) were used. An electronic flash tube substituted for lantern and shutter permitted exposures of 1/5000 second.

11. Measurements of stereoscopic thresholds were given directly in terms of angular disparity—the true measure of the stimulus to stereopsis.

12. The psychophysical method of constant stimuli was used to determine the stereoscopic thresholds.

Instrumentation

The basic instrument used for this series of experiments has already been described elsewhere [13-15] (Fig. 1). The subject's head is held in constant position by a suitable chin cup † and head rest. His eyes fixate a plumb line at a 50 cm. distance, in symmetrical convergence. He sees by reflection from the 50% reflecting-50% transmitting mirrors (M-M) a vertical polished steel needle, the test object, located also 50 cm. from the eyes. The needle is adjusted to be seen ½ arc degree to the right of the fixation plumb line. The two mirrors are so arranged that they can be turned about vertical axes in directions opposite to each other when activated by suitable levers and a screw device. When these mirrors are turned through a small angle, the images of the test needle as seen by the two eyes become disparate relative to the images of the fixation line and the binocularly perceived image of the needle is seen to move in depth. By means of the dial indicator, the amount of rotation of the mirrors and therefore the angular disparity between the images of the test object for the two eyes can be read directly. The advantage of this

† Previous studies showed that, with a head support with four button rests adjusted to the head, no difference in the results was obtained whether a wax bite or the chin cup was used.

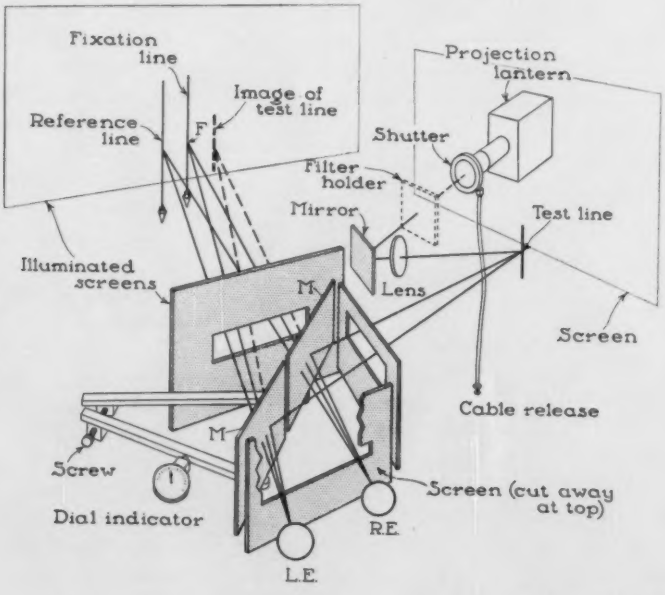

Fig. 1. — Schematic drawing of the apparatus used to determine stereoscopic thresholds with duration of the stimulus.

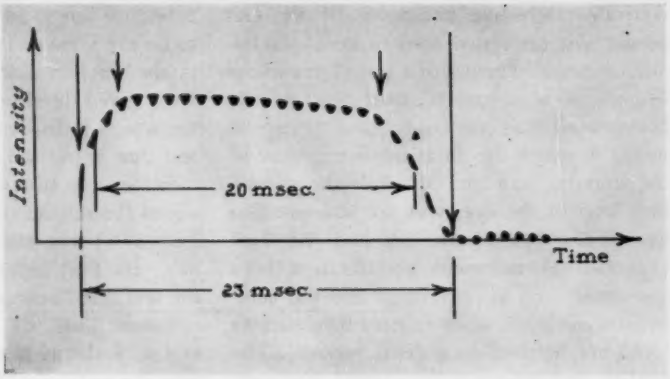

Fig. 2.—Illustration of oscilloscope trace from which the speed of the photographic shutter could be determined.

haploscopic arrangement is that the same test object is used for both eyes, and, as the disparity between the images is changed, the images do not change brightness, angular size, or their optical distance. Thus there is no change in the stimulus to accommodation. Other empirical perceptive factors related to the test object itself are thus avoided.

The test needle (line) is illuminated by light from a projection lantern, reflected from a mirror, and then focused by a cylindrical biconvex lens. All stray light from this arrangement is screened from the room. Neutral tint filters can be inserted in the beam of light to reduce the illumination of the needle.

A self-setting photographic shutter, which is activated by a long cable release and operated by the subject, is placed over the lens of the projector.

Considerable difficulty was experienced in obtaining photographic shutters whose performance could be relied on, especially for speeds shorter than $\frac{1}{50}$ second. The shutter speeds were measured by photographing the trace on an oscilloscope caused by the response to light passing through the shutter falling on a photoelectric cell. The trace was pulsed at various frequencies, to provide the scale for calculating the speeds. Figure 2 shows a typical trace for one shutter speed. The sharp rise and fall of the total light passing through the shutter compared to the total time the shutter is open are most satisfactory. The shutter speeds were also checked photographically by measuring the trace of a light image on a rotating film. Shutters were found with which the following speeds could be consistently obtained: 1, 1/2, 1/5, 1/17, 1/25, 1/46, 1/86, and 1/133 second.

The fixation, reference, and test lines were seen by the subject against a distant white smooth screen, uniformly illuminated by five 40 watt fluorescent (de luxe warm) lamps. Measurements with a McBeth illuminometer made through the mirrors at the eye position showed the luminance to be 32 millilamberts. Two 7 watt fluorescent lamps, mounted in tubular housings, illuminated the large screen with aperture just beyond the mirrors, so that its luminance would be the same as that of the background, seen through the aperture. Thus, the light-adaptation level for the eyes of the subject was uniformly maintained at a normal scotopic level of illumination. The background for the test needle was a black mat screen located at some distance from the instrument.

The equivalent luminance of the test needle was determined with the open shutter set on "time," and then neutral tint filters of increasing density were inserted before the lantern, until the subject first reported that he could barely see the needle against the white background. A combination of a 1% filter and a 25% filter gave this minimal luminance for perceptibility. The

equivalent effective luminance of the test needle was calculated then to be about 160 millilamberts. The use of a test object whose brightness was greater than that of the background was necessary in the experiments in which the duration of exposure of the stimulus was studied, while the adaptation level of the eyes was not altered. The use of the bright test line and the dark (silhouetted) reference and fixation lines was considered an advantage for the comparison of depth, since relative brightnesses could not be used as a depth motive. The fixation and reference lines could, however, be illuminated when desired to the same brightness as the test line by a second projector. Critical tests showed that changing the fixation and reference lines from dark to light had essentially no influence on stereoscopic acuity.

For the exposure time of 1/5000 second a Sylvania electronic flash lamp was substituted for the projection lantern.

The dial indicator was calibrated (1) by measuring directly the displacement of the reflected image of the needle for given changes in dial setting observed through a telescope against a distant scale and (2) by having the subject himself adjust the screw until the stereoscopic image of the test needle coincided with a reference needle placed at various accurately measured distances nearer and farther than the fixation line. The equivalent angular disparities between the two eyes were then computed by means of the usual formulas.

The apertures in the three screens used restricted the length (height) of the fixation, reference, and test lines as seen by the subject to 3 cm. at the 50 cm. distance, that is, to an angular vertical length of about 3½ arc degrees.

Procedure

To determine the stereoscopic thresholds a psychophysical stimulus-response curve was obtained with use of the method of constant stimuli and of the forced-choice, two-category type. To elaborate, suppose the reference line is adjusted so that it appears to be the same distance from the subject as is the fixation line. With the shutter set for a given duration of exposure, an operator selects a disparity for the images of the test line, using the screw to adjust the dial indicator to a certain reading. At a "ready" signal the subject trips the shutter, while he fixates intently the center of the fixation line. He then reports whether he had seen the test line "nearer" or "farther" than the reference line. By trial and error the operator finds a range of disparities such that the end-points consistently give a reasonably high percentage of "far" and of "near" responses. This range is then divided into four equal steps. The operator proceeds to adjust the disparity at these five positions in random order, until 20 presentations for each of the five disparities, 100 observations in all, have been given to the subject. A short rest period is usually given at the end of the first 50 exposures. The interval between successive exposures is always longer than five seconds, since shorter intervals might influence successive responses.[16,17] To each presentation the subject must respond "nearer" or "farther," and he is forced to guess if he is uncertain. The number of "far" and "near" responses for each step is then tallied. From these the percentage of "near" responses for each step is calculated.

When these percentages of "near" responses are plotted against the dial disparity setting, a typical psychometric sigmoid curve is obtained (for example, Fig. 3*A*). When these responses are plotted on probability graph paper, the data can be described by a straight line (Fig. 3*B*). From this line, either by inspection or, better, by calculation,‡ the dial disparity setting corresponding to the 50% level is obtained. This level corresponds to the most probable dial setting for which the test line appears the same

‡ Routinely, calculations were made for all sets of data with use of the method outlined by Berkson.[27]

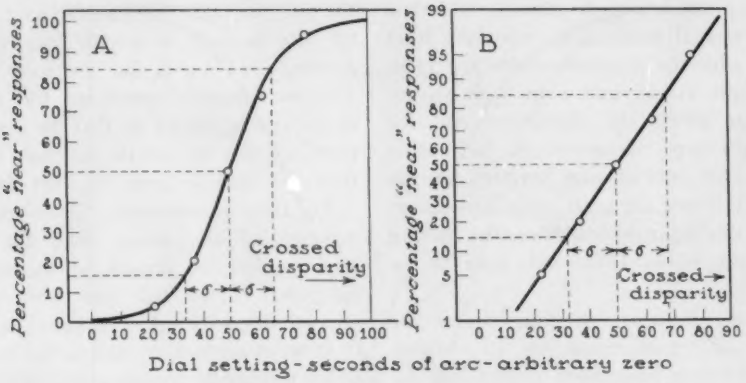

Fig. 3.—Illustration of typical psychometric curves obtained.

distance from the subject as does the reference line. More important for this study, however, is the determination of the slope of the line that best describes the data. The steeper this line the higher the stereoscopic acuity and, conversely, the lower the threshold of stereoscopic depth perception. Now, for that dial disparity setting which corresponds to the 50% level the response is 50% "near" and 50% "far," and this is the point where all response might be said to be pure guess. The difference in disparity between this point and one corresponding to the 50% level of response to a "near" stimulus would correspond to the 50% threshold or, better, "limen." Since the data obtained are fitted to the normal probability cumulative curve, and since this curve is uniquely described by the parameter σ, which is the standard deviation of the distribution, σ, in seconds of arc, is used as the measure of the threshold, or limen, in this paper. On the graph the separation of the disparity points corresponding to the 84% and the 16% levels is 2σ and, as such, is the range within which the stimulus is reported "near" about 68% of the time.

Three subjects were used in the tests, one highly experienced in depth discrimination, one with considerable experience, and one with no previous experience. The latter two were nonpresbyopic and essentially emmetropic. The first subject used a +1.50 sphere before each eye to compensate some presbyopia.

Results

All subjects reported that with short exposure times of the test line the depth impression seemed to follow instantaneously. There seemed no delay between the moment of exposure and the following depth response, such as might be expected if a central or cortical elaboration of the stimulus was required before the experience of stereoscopic depth emerged. This is contrary to such reports as that of Pauli,[18] who found that, when drawings in a stereoscope were used, a reaction time of nearly one and one-half seconds was required before the complete emergence of depth was experienced. Our subjects, with the longer exposures of one-fifth second to one second, even found it difficult at first to wait for the end of the exposure time before wanting to make a decision. With short exposures the decision had to be made immediately following the exposure, for the perception of depth would fade quickly. Strict attention to the fixation point and the maintenance of a "set" to experience depth with these short exposures were necessary. Any wandering of attention to other features of the test, such as brightness, lateral position, and so forth, seemed to interfere with the response to depth. It is true, however, that, in surroundings in which there

are many objects that provide empirical clues to spatial localization, especially if in conflict with the localization derived from stereoscopic vision, and even with stereograms in which the disparities may be abnormally large, the stereoscopic perception of the whole field of view may not emerge at once.[19] There are great individual differences in this regard; sometimes even as long a time interval as 15 seconds may be required.

Both the influence of fatigue and the evidence of improvement due to learning during the test have been emphasized by other writers. In the present experiment many correlations between the first and second 50 exposures of a number of sets of data showed little effect of fatigue, but there was some evidence of learning in that a smaller σ might be found with the second half. Frequently it was found, moreover, that data taken in the latter part of the afternoon, when the subject was less alert, gave a higher threshold (σ) than when the same test was given in the morning.

One would expect some natural variation in the thresholds to occur at different times even when the same test was used. To gain some idea of this variation the same test was repeated five different times by one subject (exposure of $\frac{1}{25}$ second, luminance of test line 40 millilamberts, and reference line 3.5 mm. nearer than the fixation point). The mean disparity for the five sets of data gave a threshold, or limen, of stereoscopic depth (σ) of 29.6 seconds of arc, with a standard deviation about this value of 4 seconds of arc; this was a range of between 25.9 and 34.3 seconds of arc.

A. Comparison of Thresholds by Two Methods.—It had been suggested that thresholds might better be obtained by a one-category, constant-stimulus method. In this method two experiments are necessary, one pertaining only to "nearer" responses and one pertaining only to "farther" responses. The steps of disparity are so chosen in the first that, following the exposure, the subject reports whether he saw the test line "nearer" than the fixation point or "not nearer"—a simple "yes, it looked nearer," or "no, it did not look nearer." For the second experiment the steps of disparity are chosen so that the subject reports whether he saw the test line "farther" than the fixation point or "not farther."

For these experiments, the reference line was set 3.5 mm. nearer than the fixation line, so that the images of the reference line and of the test line were seen in crossed disparity. A 25% filter was used in front of the lantern, and so the luminance of the test needle was about 40 millilamberts. A constant exposure duration of $\frac{1}{25}$ second was used.

First, the two-category "near" or "far" method, as described previously, was used to establish the 50-50 neutral point. Curve *A* in Figure 4 shows the computed curve based on the average of three sets of data. The dial indicator reading (arbitrary zero) corresponding to the most probable value for which the test needle appeared the same distance as the reference line was 82 (seconds of arc). We could normally assume that, when the dial indicator was set at this reading, the response of "near" or "far" resulted from pure guess.

For the "near" or "not near" experiment, the beginning step of the range in crossed disparity would be close to this 82 dial setting, and the five steps in the constant-stimulus presentation would be above this point. Curve *B* of Figure 4 shows the average results of two sets of data. Similarly, for the "far" and "not far" data the five steps in the test would be for disparities below the 82 dial setting. Curve *C* (Fig. 4) shows the average results of two sets of data.

These three sets of data are of special interest. They show, in the first place, that the 50% threshold of responses, *PR* for "near" and *PQ* for "far," corresponds to the 75% level *R'* and *Q'* on the "near" or "far" curves, respectively. This shows that the "near" or "far" two-category, forced-

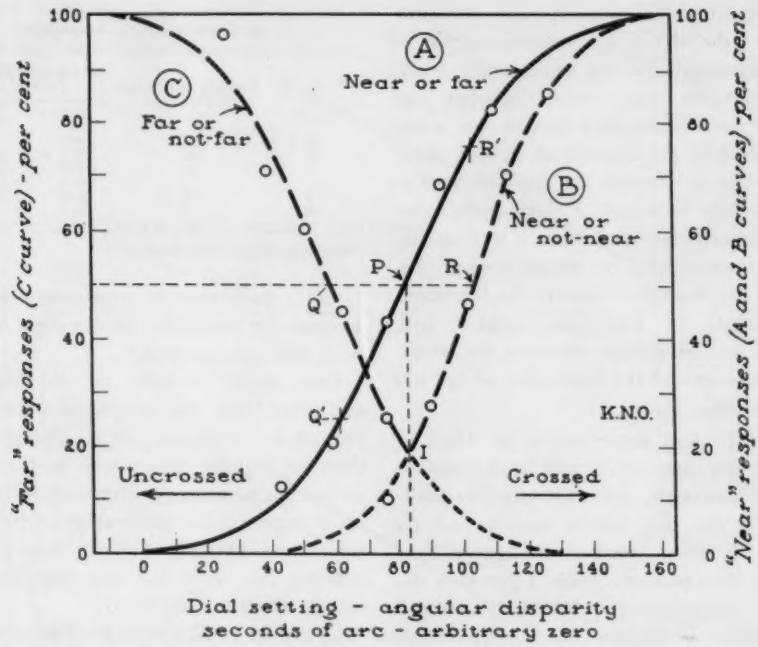

Fig. 4.—Data used to illustrate the relationships between three psychometric methods of determining stereoscopic thresholds.

choice method yields the same measure of threshold as does the one-category method.

More important, however, is the following: If point *P* on the "near" or "far" curve indicates the disparity to which the subject reports "near" or "far" on the basis of pure guess, he is not perceiving stereoscopic depth at this disparity and one would expect the lower "tails" of Curves *B* and *C* to be nearly zero percentage at this 82 dial setting. However, both of these curves show nearly 20% response "near" or "far" at this disparity and occasional responses even for disparities differing from this by 30 seconds of arc. This result suggests that the subjective criterion of a given depth response itself fluctuates statistically about a mean disparity and that the 50% level is not the disparity corresponding to pure guess.

The corresponding curves of the other two observers were less symmetrical in that the 50-50 point of the "near" or "far" (*A*) curve did not coincide precisely with the intersection of the other two curves. These differences, however, do not change essentially the argument given here.

These results cannot be explained on the basis of the small unsynchronized physiologic nystagmoid movements of the two eyes, since the disparity between the test object and the fixation point would be independent of the positions of the eyes. The result cannot be explained by errors in the setting of the disparity on the dial indicator, since this setting can be made with a maximal error of about 4 seconds of arc disparity.

B. Stereoscopic Thresholds for Different Luminance Contrasts, with Constant Short Exposure Time.—It would be natural to think that in any threshold experiment the effect of a decrease in duration of a stimulus could be compensated for by an increase in the intensity of the stimulus. Similarly for these experiments, the relationships between

the duration of stimulus exposure, the luminance of the test object relative to that of the background, and the stereoscopic acuity must first be determined. Mueller and Lloyd [20] have shown that stereoscopic acuity increases with an increase of luminance of the background field in the same manner as visual acuity increases, a relationship that would be expected if ultimately stereoscopic acuity must depend on visual acuity. Reports to the contrary found in the literature, for example, by Rady and Ishak,[21] usually fail to discriminate between the adapting luminance and the luminance of the test details alone.

In the present experiments the level of the adapting luminance was kept constant at 32 millilamberts, while the effective luminance of the test needle was varied by means of filters in front of the lantern, thus reducing the contrast. Table 1 presents the data for the stereoscopic thresholds obtained under these conditions for a $\frac{1}{25}$-second duration of stimulus exposure. Inspection of this Table shows that for all three subjects the stereoscopic threshold was essentially unchanged over a fivefold change of luminance of test line. At the contrast level of 1.03, stereoscopic depth could not be seen.

Similarly, Table 2 shows the stereoscopic thresholds when an electronic flash tube was substituted for the lantern and the exposure time was 1/5000 second. These results show, then, that a two-hundred-fifty-fold change in luminance of the test object is not a parameter in stereoscopic acuity as long as the luminance of the light-adapting field remains constant.

TABLE 1.—*Influence of Contrast of Test Detail to Background on Stereoscopic Thresholds* *

Filter, % Transmission	Equivalent Luminance of Test Needle, Millilamberts	Contrast	Stereoscopic Thresholds, Seconds of Arc		
			Subj. 1	Subj. 2	Subj. 3
None	160	5	21.6	25.0	27.7
50	96	3	24.4	24.2	30.8
25	64	2	24.7	36.6	25.3
10	45	1.4	28.9 24.2	20.1	21.9
5	36	1.1	26.4 32.7	22.3 34.2	24.0 24.7
1	33	1.03	--	--	--

* Exposure time, 1/25 second.

TABLE 2.—*Influence of Contrast of Test Detail on Stereoscopic Thresholds* *

Filter, % Transmission	Relative Luminance of Test Line	Stereoscopic Thresholds, Seconds of Arc	
		Subj. 1	Subj. 2
25	250	29.5	34.6
10	100	33.3	35.6
5	50	43.1	--
		40.1	
1	10	40.3	27.5
0.1	1	35.4	32.3

*Exposure time, 1/5000 second.

One must conclude, as did Geblewicz and Shen,[8] that the peripheral sense organs require a certain amount of energy to initiate an impulse which will be transferred to perceptual centers. But the central processes required for elaboration of the stimulus, once started, follow their courses without the need for any supplementary energy from the stimuli.

C. Effect on Stereoscopic Threshold with Change in Duration of Exposure of Test Object.—The data of the preceding section have shown that when the duration of exposure of the test object is short the threshold of stereoscopic depth is relatively unaffected by change in contrast of the test object, as long as the retinal luminance-adaptation level remains constant. Thus, in studying the influence of exposure time alone on the threshold of stereoscopic vision, we need not consider as a variable the fact that the shorter the exposure time the less light there is reaching the retina.

Data were obtained with the procedure outlined above and in which the only variable was exposure time. Data were taken when the reference line was (1) in the apparent frontoparallel plane of the fixation line, (2) in front of that plane, and (3) behind that plane. The latter two sets of data give us information as to whether the effect of exposure time is different when both reference and test lines are seen in crossed or uncrossed disparity. The results are shown graphically in Figures 5 and 6. In these the logarithm of the exposure is

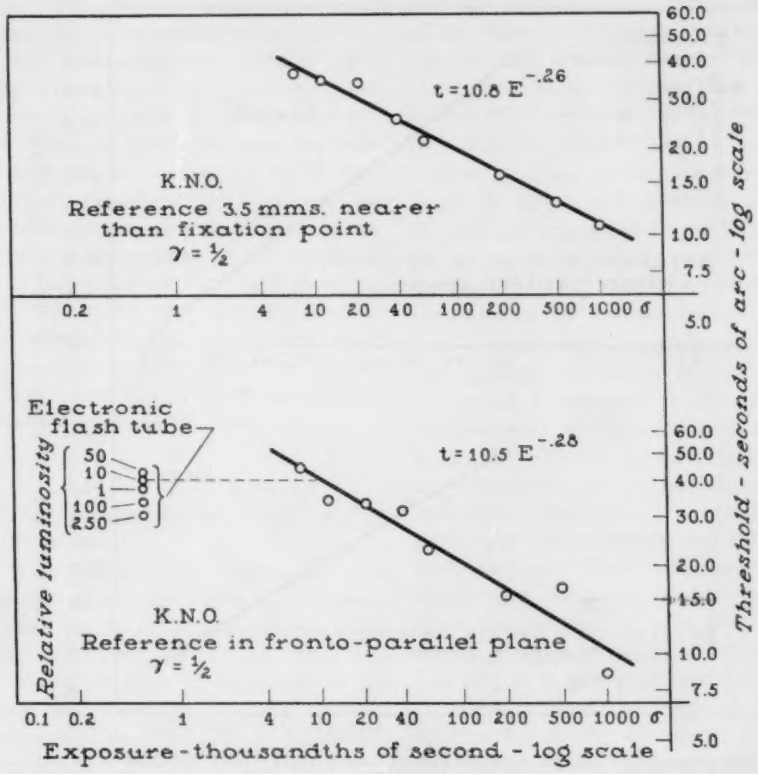

Fig. 5.—Graphic illustration of data showing relationship between stereoscopic threshold and duration of exposure of the stimulus for one observer.

is plotted on the abscissa and the logarithm of the threshold of stereoscopic depth in seconds of arc (σ) is plotted on the ordinate. There is no basic reason why the ordinate is plotted on a logarithmic scale except that when it is so done the data can be adequately described by a straight line.

Inspection of these graphs shows that within the range of exposure times from 1 second to 1/200 (0.005) second there is a marked increase in stereoscopic threshold, from about 10 seconds of arc to 40 seconds of arc, a fourfold increase. As the exposure time decreases the threshold increases, slowly first and then more and more rapidly. Within the range of exposures used, therefore, the change in angular disparity threshold, t, associated with decreased exposure times can be adequately described by the relationship $t = t_0 E^{-a}$, in which t_0 is the threshold for an exposure of one second, E is the exposure time, and a is a constant that describes the rate at which the threshold increases with decrease of exposure times. For the three persons who served as subjects here the constant a is of the order of 0.3.

The supplementary measurements in which the lantern was replaced by the electronic flash lamp (rated duration of exposure being 0.0002 second) suggest that, for exposures shorter than 0.005 second, the stereoscopic threshold levels off to a constant upper value.

It is also to be expected that there is a lower limiting threshold for exposures longer than one second (which is the threshold for a continuous exposure). Since the

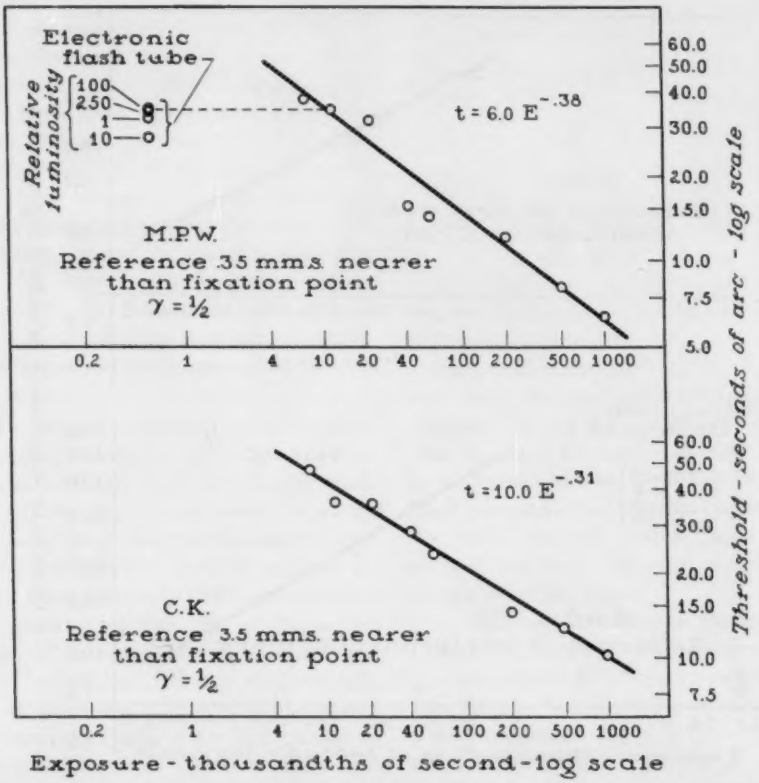

Fig. 6.—Graphic illustration of data showing relationship between stereoscopic threshold and duration of exposure of the stimulus for two other observers.

constant-stimulus method used here to obtain a measure of thresholds is not suitable for long exposures, no data for exposures greater than one second were obtained. Adjustments of the test line by the subject himself for continuous illumination were made, but one cannot compare the data from such settings with the data obtained using the method of constant stimuli.

D. Effect of Constant Disparity of Reference and Test Lines.—When the reference line is placed nearer or farther than the fixation point, the images in the two eyes of both that line and the test line will be disparate. Since the lateral angle of both the reference and the test line is only ½ degree, large displacements of the reference line farther or nearer than the fixation point cannot be used, because of the limited range within which stereopsis is possible at all.[22]

Table 3 shows the results of data that were obtained when the reference line was located at three different positions. This is sufficient to ascertain whether the stereoscopic depth thresholds and the general behavior of stereopsis are different when the

TABLE 3.—*Stereoscopic Thresholds When Reference and Test Lines Are Seen with Disparate Images* *

Position of Reference Line	Subject 1		Subject 2		Subject 3	
	t_0†	a	t_0†	a	t_0†	a
3.5 mm. nearer	10.8	0.26	6.0	0.38	10.0	0.31
Fixation plane	10.5	0.28	6.6	0.31	—	—
6.0 mm. farther	13.4	0.24	10.0	0.28	10.4	0.31

* The effect is in terms of the relationship $t = t_0 \exp(-a)$ in which t_0 is the threshold measure for one-second exposure and a is the exponential rate of increase of threshold with decrease in exposure time.
† Seconds of arc angular disparity.

disparities between the images are small (reference line at same distance as the fixation point) from what they would be when the disparities are large (reference line nearer or farther than the fixation point). In this Table are given the basic threshold, t_o (seconds of arc), obtained for a one-second exposure and the rate, a, at which the threshold increases with decrease in exposure time, as determined in the preceding section. Inspection of the Table shows no marked differences depending on whether the reference line was nearer or farther than the fixation line. Since no marked effect was found, the problem was not systematically studied any further.

Comment

We can summarize the results of this study as follows:

1. With constant luminance adaptation, the contrast of the test object has relatively little effect on the stereoscopic threshold, as long as the stimulus can be seen. That is to say, for a given level of luminance of the adapting background, stereoscopic acuity is independent of the luminance of the objects seen in depth.

2. Under constant conditions of adaptation there is a fourfold increase in stereoscopic threshold associated with a decrease in the duration of the exposure of the test object between 1 second and $\frac{1}{125}$ second. Thus, stereoscopic acuity rapidly deteriorates with decrease in the exposure time of the test object. The threshold appears to be related to exposure time as an exponential function of that exposure time. As the exposure time decreases, the increase in threshold is slow at first and then becomes more and more rapid as the exposure time decreases further, up to a limit of about $\frac{1}{125}$ second. For still shorter exposures the threshold appears to reach an upper limiting level of about 40 to 50 seconds of arc.

3. The increase in stereoscopic threshold with decrease in duration of exposure time appears to be independent of whether or not both reference and test objects are seen with disparate images. That is, the course of the stereoscopic response is no different whether the objects observed are in the same plane as the fixation point (and the horopter) or are considerably nearer or farther than the fixation point.

How shall we account for these results? Since the threshold function is independent of contrast, we need not look for an explanation in terms of the amount of light energy (the I×t relationship) available to the retina as the exposure time decreases.

The more probable explanation lies in the role played by the normal ocular nystagmoid or tremor movements of the eyes in the maintenance of perception and visual acuity.[23-25] These involuntary movements are to a certain extent random, or at least aperiodic. The relatively large involuntary drifts and jerky motions are synchronized in the two eyes. There are, however, smaller involuntary tremor movements that are independent for the two eyes, that have varying frequencies up to about 100 per second, and that have excursions the median extent of which is about 15 seconds of arc. These movements of the eye cause proportional movements of the image on the retina, so that the image of an observed object will actually be continuously moving over a number of retinal elements. This fact has been used to explain in part the much greater resolution of the eye, when measured, than can be accounted for on the basis of the size of the dioptric image on the retina and the structural dimensions of the retinal elements.

The average extent of the excursions of the eye, which would occur in short intervals of time, will be less the shorter the exposure. Under normal laboratory conditions Riggs, Armington, and Ratliff [26] have measured the average extent of these excursions during short intervals of time. For example, with use of a flash interval of 1/100 second the retinal image moved as much as 5 seconds of arc in 38% of the excursions and as much as 10 seconds of arc or more in only 10% of the excursions. Exposures of

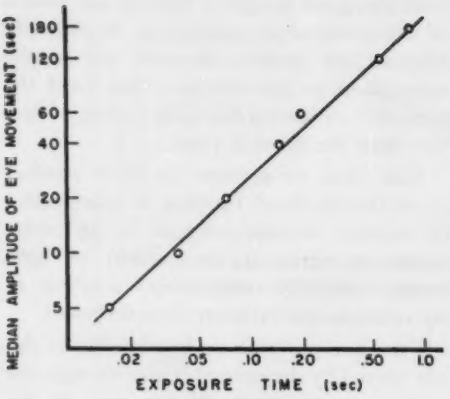

Fig. 7.—The relationship between median amplitude of excursions of eye movements in seconds of arc and the exposure time. (Reproduced with permission from Riggs, Armington, and Ratliff,[36] *Journal of the Optical Society of America*, American Institute of Physics, New York.)

1/10 second have included movements of 20 to 40 seconds of arc. For exposures of one second occasional excursions may reach 3 minutes of arc. When Riggs, Armington, and Ratliff plotted the mean eye movement excursion (log scale) against the log of exposure time, the data fell on a straight line (see Fig. 7, which is reproduced from their paper). A comparison of Figure 7 with Figures 5 and 6 of this paper is of special interest.

The argument would be that the stereoscopic acuity is enhanced in some relationship to the number and extent of the excursions of these involuntary eye movements that have taken place during the exposure of the test object. For very short exposures, shorter than 1/200 second, the retinal image is "stopped," and, correspondingly, one would expect that there would be an upper threshold of stereoscopic vision. This explanation is entirely consistent with our results showing that the stereoscopic threshold is independent of both contrast of the test object and disparity of the images. This hypothesis, that the deterioration of stereoacuity with decrease in exposure of the stimuli is due to the decrease in the number and extent of the physiologic nystagmoid movements that will occur during a given exposure time, is consistent with the well-recognized theories that these movements, within limits, normally enhance visual acuity. In stereoscopic vision the theory implies that the involuntary nystagmoid movements, causing the displacement on the retina of the images of the fixation line, the reference line, and the test line, enhance the discrimination of relative mean directions of those images.

Since the pattern of these movements will undoubtedly be affected by extraneous influences, such as unusual straining or special attention on the part of the subject to hold fixation as steady as possible, variations in the thresholds, apart from normal physiologic variations, will be expected from time to time in such a series of experiments as those reported here.

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Spiral Visual Fields

Statistical Analysis of Eighteen Cases Found in a Survey of Eight Hundred Unselected Eye Patients at a State Medical Center

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Introduction

Spiral fields can be elicited only when the radii of the visual fields are tested in a systematic clockwise or counterclockwise manner; they contract like coil springs, although they may unwind after reassurance and encouragement. If the visual fields are tested differently, several varieties may be obtained. Thus, if opposite ends of the vertical and horizontal diameters and the two ends of the two oblique meridians of the visual field are tested, the eight points obtained may result in a four-pointed star. The shifting field of Förster refers to the field which is wider on the side on which the test is begun.[3] Thus, if we begin on the nasal side and cross over to the temporal side, through the fixation point, the test object will be seen for a greater distance on the nasal side and will disappear more quickly on the second, or temporal, side. If the method of taking the field is reversed, the findings are reversed; the test object will be seen for a greater distance on the temporal side, where it is first presented, and for a shorter distance on the nasal side, where it is seen secondarily.

Wilbrand's exhaustion field results from essentially the same method applied only to the horizontal meridian.[17,18] The smallest field that can be obtained has been called the "minimal visual field," and the largest at the beginning of the examination, the "maximal visual field."[7] The cause of spiral fields is not known. Traquair[16] listed neurasthenia, anxiety neurosis, and traumatic neurosis; fatigue also has been incriminated.

Materials and Methods

We quote from a previous paper,[11] which reported on the tubular fields of hysterical amblyopia. The statistical data for both reports were obtained at the same time and by the use of the following methods:

Eight hundred unselected eye patients, with various complaints and diagnoses, were examined. The routine examination for the purpose of this study was as follows: Visual acuity was taken without and with glasses. If glasses improved the vision by as much as one line, the patient was examined perimetrically with glasses on.

The examination was standardized for all patients as follows: The tangent screen was explained to the patient. The fixation point for patients with normal vision was a gray disc, 1 cm. in diameter, with a black-headed pin at the center. For those with poorer vision, white discs, of increasing size, held by a black pin, were used. The patient was seated on a stool with his head fixed in a chin rest. The right eye was tested first unless the vision in that eye was less than that of the left eye. A trial run on the blind spot was done to instruct the patient and to demonstrate the method. The examination was done at 2 meters from the screen, using a 10 mm. white test object. The test was started on the temporal side of the horizontal meridian. The test object was moved in from the blind to the seeing area. Subsequent radii at intervals of 30 degrees were tested, the test being conducted around the screen in a clockwise manner.

After the two eyes had been examined separately at 2 meters, the patient was moved up to 1 meter from the screen and the test repeated, with use of a 5 mm. white test object to provide a constant angular size.

After the perimetric examination, the corneal sensitivity of each eye was tested with a sterile cotton wisp as the patient fixed his gaze straight

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ahead. The patient's lids were held open, and the wisp of cotton was brought in from the temporal side, out of the field of vision, to touch the cornea. If the patient made no lid response and claimed no feeling, the corneal sensitivity was graded 0. If the patient made no response but said he did feel something vaguely, the sensitivity was graded 1. When there was a lid response and/or a definite sensation of touch, the sensitivity was graded 2. Lacrimation and/or a definite sensation of discomfort was graded 3, and a complaint of pain and withdrawing movement of the head, 4.

If the patient was found to have tubular or spiral fields, perimetric examination was done, using a Ferree-Rand perimeter. A 3 mm. white test object was used at 330 mm. Two weeks later the patient was reexamined on the tangent screen. If the result was still positive, another examination was made after a lapse of two more weeks. On this third visit the method of testing was reversed in three of its details: (1) The left eye was tested first; (2) the test object was moved centrifugally (from the seeing to the blind area), and (3) the test was conducted in a counterclockwise, rather than a clockwise, manner.

Results

Incidence.—As a result of this survey 42 cases of the tubular fields of hysteria were uncovered, and a statistical evaluation of these has been reported.[11] We shall now report our findings regarding the patients with spiral fields which were discovered by this survey. Of the unselected eye patients tested by the above technique at Indiana University Medical Center, 18, or 2.25%, were found to have spiral fields. The incidence was much higher among institutional cases from penal institutions (6.40%) than among noninstitutional cases (1.34%) (Table 1).

TABLE 1.—*The Sex Distribution of Spiral and Control Fields (but Not Tubular Fields) as Found in a Survey of 800 Unselected Eye Patients with Division into Institutional and Noninstitutional Cases*

	Sex	Spiral		Control	
		No.	Per Cent	No.	Per Cent
135 institutional cases	M	8	6.45	112	90.32
(124 males & 11 females)	F	1	9.09	8	72.73
	Both	9	6.67	120	88.89
665 noninstitutional cases	M	2	0.69	282	97.24
(290 males & 375 females)	F	7	1.87	347	92.53
	Both	9	1.35	629	94.59
Total		18	2.25	749	93.62

Thirteen of these eighteen patients had bilateral spiral fields; three had tubular fields in one eye and spiral fields in the other; one patient had one eye patched and not available for study. In this study of clinic patients tubular fields were found to be commoner (5.25%) than spiral fields (2.25%), whereas in the private practice of ophthalmology spiral fields of a mild type have been seen much more frequently than have tubular fields.

The Confrontation Test and Spiral Fields. The confrontation test was performed routinely on the last 525 patients of the 800 unselected eye patients studied. It was used as a test preliminary to other field studies to determine whether this simple test could serve as a reliable screening technique. It was done with moving fingers brought in centripetally from the blind to the seeing area. If contraction of the visual field was obtained, the test was repeated after approximately doubling the distance from the patient in order to determine whether the fields were tubular in character. Seven patients with pure spiral fields demonstrated a contraction of their confrontation fields, but not a single one gave fields which were tubular in character when checked at the greater distance.[11] In each of the five cases in which spiral fields developed into tubular fields, the negative confrontation test became positive. It is interesting that the confrontation test became equivocal or suggestively positive but not typically so during this period of transition.

Classification of the Degree of Contraction of Spiral Fields.—In the figure are diagrammed three classes of spiral fields: 1. Mild—the spiral contracts down to or near the fixation point within three or more

Severity of spiral fields. Left, mild (three or more turns); center, moderate (within two turns); right, severe (within one turn).

TABLE 2.—*The Frequency of Spiral Fields Grouped According to the Severity of Contraction*

Grade	Spiral Fields	
	No.	Per Cent
Mild *	4	22.2
Moderate †	5	27.8
Severe ‡	9	50.0

* Contraction to or near fixation point in three or more turns.
† Contraction to or near fixation point within two turns.
‡ Contraction to or near fixation point within one turn.

360-degree turns. 2. Moderate—the spiral contracts to or near the fixation point within two complete 360-degree turns. 3. Severe—the spiral contracts to or near the fixation point within one 360-degree turn.

Among clinic patients we have found the severe type of spiral fields to be the commonest (Table 2), whereas among private patients the mild type has been most commonly observed.

Change in the Type of Field with Time.—Of the original 800 unselected patients, 35 with either spiral or tubular visual fields were seen two or more times. Of these, 13 showed a change in the type of their fields during the period of observation; this change is depicted in Table 3. We have noted spiral fields at 1 meter after eliciting tubular fields at 2 meters. The opposite has also been observed, in that a patient may have spiral fields on his check at 2 meters but tubular fields when checked at 1 meter.

Corneal Sensitivity in Patients with Spiral Fields.—As previously reported, corneal sensitivity is not significantly altered in patients with spiral fields, in contrast to a statistically significant reduction in corneal sensitivity observed in patients with hysterical amblyopia.[11]

TABLE 3.—*Change in Type of Visual Fields Observed in Thirteen Patients*

Change in Fields *	Cases, No.
T⇄S	1
T→N	2
T&T→S	1
T&S⇄N	1
S⇄T	4
S⇄N	4
N→S	3
	14 (13 patients)

* T, tubular; S, spiral; N, normal.

The Role of Age in the Incidence of Spiral Fields.—The number of cases is inadequate for accurate appraisal.

Effect of Method of Taking Field.—Only one patient with spiral fields returned for the third visit, during which the test object was moved centrifugally and in a counterclockwise manner. There was no change in the visual field obtained except that the spiral developed in a counterclockwise instead of in a clockwise manner.

The Role of Time of Day in the Incidence of Spiral Fields.—Spiral fields have frequently been called fatigue fields. For this reason, the time of day that the field examination was done was recorded, with the aim of determining whether spiral fields occurred with more frequency at certain times of the day. No such relationship was found among the 18 spiral-field patients studied (Table 4).

The Duration of Spiral Fields.—Fourteen of the eighteen patients with spiral fields returned for a second examination. Of these, the fields of five became normal after from 9 to 23 days; three remained spiral in type; and seven had changed to tubular after 1 to 4 weeks.

Concomitant Organic Factors in Patients with Spiral Fields.—Only 3 (16.6%) of the 18 patients with spiral fields had concurrent organic ocular conditions. This may be compared with the 15 (35.7%) of the 42 tubular-field patients with concurrent organic ocular conditions.

The Presenting Complaint of Patients with Spiral Fields.—Poor vision was the commonest complaint recorded. Complaints of "holding reading matter too close," "headache," and "black-out spells" were also encountered.

TABLE 4.—*Effect of Time of Examination on the Frequency of Spiral Fields as Compared with Control Fields*

Time of Day	Controls, No.	Spiral Fields, No.
8–10 a.m.	281	7
10–12 a.m.	143	3
1– 3 p.m.	286	6
3– 5 p.m.	39	2
Total	749	18

TABLE 5.—*Best Corrected Visual Acuity of Tubular and Spiral-Field Cases*

Visual Acuity	Tubular Fields, No.	Spiral Fields, No.
20/15	3	2
20/20	17	8
20/25	5	2
20/30	4	3
20/40	3	1
20/50	1	0
20/60	2	0
20/70	1	1
20/100	1	1
20/200	4	0
20/400	1	0
Total	42	18

The Visual Acuity of Spiral-Field Patients.—From Table 5 it can be seen that 10 (55%) of the 18 patients with spiral fields had a vision of 20/20 or better. The visual acuity of the remaining spiral-field patients was not as greatly reduced as the visual acuity of the patients with tubular fields.

Comment

Spiral fields are frequently known by the synonyms of fatigue or neurasthenic fields. Brodie Hughes states that they are merely the result of tiring and inattention and, while commonly occurring in the hysteric, may be found in the patients who are tired and confused as the result of an intracranial tumor or some other serious and debilitating disease.[5] As pointed out by Traquair, the carry-over of contraction in the field of one eye to that of the other demonstrates that retinal fatigue is not involved.[16] Thus it is necessary to assume a central origin for spiral fields, and we are forced to doubt Wilbrand's concept that there is an insufficiency of the retina due to changed conditions of metabolism affecting the external layer[17,18] and Peters' idea that there is a disturbance of innervation in the transmission of nerve impulses from the retina to the optic tracts.[8] More plausible are the views of Placzek that there is a blunting of the center of consciousness,[9] of Simon that there is a fatigue of the psychic sphere,[15] and of Schmidt-Rimpler that inattention and lack of the power of concentration account for the contraction of the visual fields.

That fatigue plays some role is indicated by the fact that many clinicians have labeled spiral-field patients as neurasthenics. If fatigue is active it would appear to be mental or emotional rather than physical.[10]

Many authors include spiral fields in their discussion of hysteria. Both a review of the literature and a consideration of our data indicate that there are many similarities between spiral and tubular fields. Retraction of the field of vision has been considered the most characteristic stigma of hysteria since Charcot first drew attention to it in 1872.[6] According to de Schweinitz,[13] it goes without saying that the spiral visual field does not possess the form of a spiral. The narrowing takes place because the boundaries are contracted concentrically and the points at which the test object is first noticed are only the stages at which the boundary lines cut the individual meridians at the moment when the test object appears. As far as we have investigated it, we would confirm this conclusion. Von Reuss contended that all constant visual-field contractions were of hysterical character, while everything which was of a variable nature in the visual field belonged to neurasthenia.[10] This differentiation was found to have value but not to be rigidly true, as there were frequent mixtures. It was also learned that many neurasthenics exhibited no change in their visual fields, and the same was true of hysterics.

Although we routinely use the tangent screen instead of the perimeter and do not have a large series, we have not confirmed the findings of Hurst and Symns that an outward spiral is always obtained instead of an inward one if the white disc of the perimeter is moved outward instead of inward. In this manner they produced an inward spiral for one eye and an outward spiral for the other, or an inward spiral on one day and an outward spiral with the same eye on another day. They felt that there were no suggestions made in the method of using the perimeter, as identical results were obtained by other observers who were ignorant of the nature of the cases. Although in the study herein reported

the test object was moved in from the blind to the seeing area; in my routine perimetry the test object is moved outward from the fixation point until it disappears and is then brought inward until it reappears. Using this technique, I have seen at least 50 patients with spiral or tubular fields and have not observed that my technique has resulted in the disappearance of such fields in patients already demonstrated to have them. Also, 16 patients with tubular fields were tested differently on two separate visits without any apparent effect on the size of the tubular fields obtained.[11]

In support of the hysterical or at least the suggestible nature of spiral fields is the study on experimental malingering mentioned by Hurst and Symns.[6] Twenty-seven persons were asked to pretend that they were paralyzed on the right side as a result of a railway accident, and they were asked if they had noticed some impairment of vision in the right eye. Seven (about one-fourth) said they had some impairment. When tested with a perimeter all had a narrow field on the right side, and one had a contracted field on the left. In the only two cases in which it occurred to the authors to continue the investigation after the first field had been marked out, a spiral was obtained.

The close relationship of tubular and spiral fields is demonstrated by the fact that they can change from one to the other or change to normal fields and by the fact that the same patient may have a spiral field in one eye and a tubular field in the other. There are, however, a number of minor differences which usually differentiate patients with spiral from those with tubular fields. The most striking differences so far observed between these two groups are the absence of reduced corneal sensitivity and reduced visual acuity in spiral field patients and the fact that there is less contraction of the visual fields to the confrontation test.

The transient nature of both tubular and spiral fields is evident from the fact that they can change from one to the other or change to normal fields. Binswanger emphasized the importance of the psychic condition at the time of the examination and its effect on the visual field and insisted that patients be methodically investigated at different times with due regard not only to their power of concentration but also to their emotional state.[2] In my experience the usual progression is for spiral fields to appear first and pass through the tubular type to normal fields. The reason for this change in type of fields is not evident from our data. We have frequently observed anxiety in patients with spiral fields and with reassurance have been able occasionally to make spiral fields disappear. It is possible that spiral fields are "tubular fields in the process of development." In any event, these two types of fields are closely related.

Summary

In a survey of 800 unselected eye patients at a state university medical center the following statistical data regarding spiral visual fields were obtained:

1. The percentage from penal institutions was higher (6.40%) than the remainder (1.34%), with an over-all incidence of 2.25%.

2. The confrontation test, which in spiral field patients revealed a slight contraction of the fields of vision, was not of diagnostic value.

3. The time of day and method of performing the visual fields had no apparent effect on the incidence or on the form of the spiral fields obtained.

4. Spiral fields usually changed either into tubular or into normal fields.

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Diverging Exercises While Accommodating

A Simple Technique Using an Accommodation Card, a Prism Rack, and Plus and Minus Spheres

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Many patients with heterophoria, who appear to have fair to good amplitude of fusion with prisms when fixating on a 3 mm. white-headed pin or light at 25 cm., are unable to maintain fusion when accommodating on small print (300 mm. type for example). These patients, usually young children, are frequently found to be slow readers and manifest an overconvergence on ophthalmographic studies, particularly when shifting their fixation to the next line of print. Patients with this difficulty often improve their ability to sustain fusion for near work with a simple home exercise.

The patient is given a horizontal prism rack [1] and an accommodation card [2] (Fig. 1) with letters, numbers, and single E's graduated in size. Holding the accommodation card in one hand and the prism rack in the other (Fig. 2), the patient is instructed to fixate the smallest word, number, or E which he can fuse while accommodating (focusing the eyes in near vision). He then holds the prism rack, base in, before one eye, or base toward the nose. Beginning with the weakest prism, the patient endeavors to keep the fixated word (for example, a single letter of 1 M print) clear and single as prisms of gradually increasing strength are placed before one eye. Whenever "doubling" occurs, the patient is encouraged to fuse the two images. Blinking the eyes rapidly sometimes aids in fusing the double print, but if the diplopia remains the strength of the prism is gradually reduced until fusion is again accomplished. The exercise is continued, and an attempt is made to overcome as much base-in prism as possible (approximately 18Δ base in). It is to be noted that with the stronger prisms a slight blur, due to aberration, may be present, but this does not interfere seriously with the exercise.

The amount of prism the patient can overcome while maintaining fusion with accommodation may vary slightly from day to day in the early stages of training, but a certain stability should manifest itself in about a week. When the patient has reached the maximum base-in prism he can overcome while fixing, say, 1 M print, he is instructed to fixate the next smallest size of type and repeat the same exercise. As the patient's ability to maintain fusion while accommodating improves, the size of the print fixated is gradually reduced until he can read the smallest print possible (for example, 300 mm. type).

If corrective lenses have been recommended, the glasses should be worn during the early period of training and especially if lenses have been prescribed to lessen the accommodative effort at near. This correction may include a bifocal addition or plus spherical lenses in clip-on frames.* [3] Plastic clip-on prisms [4] are required at times to correct hyperphoria. When the patient has reached the stage where he can maintain fusion on small print and diverge while accommodating, the additional plus may be

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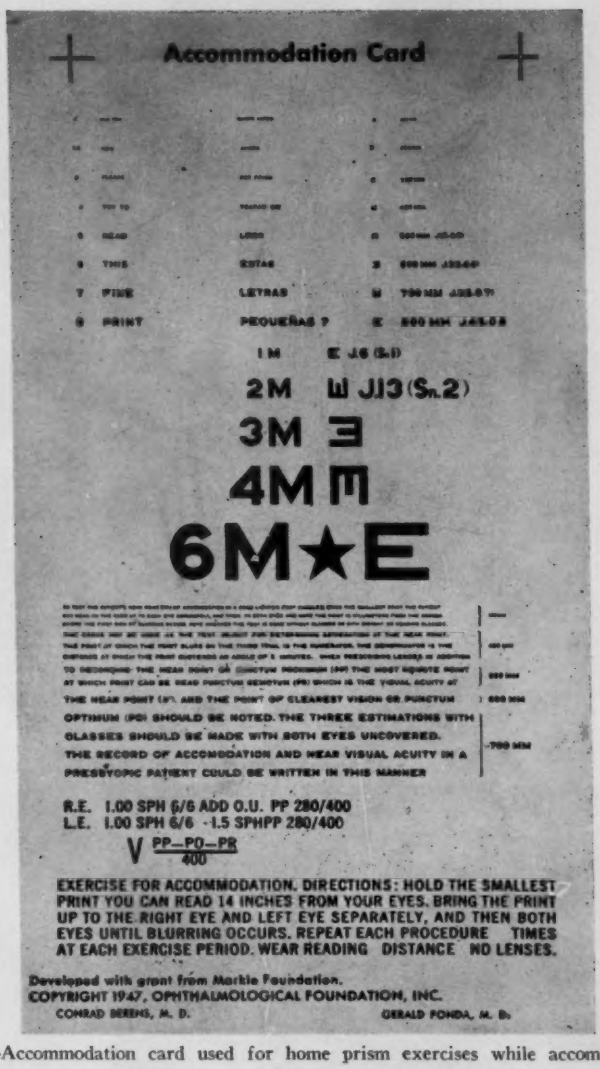
* Made by R. O. Gulden, Philadelphia 20.


Accommodation Card
1 M
2M
3M
4M
6M★E
R.E. 1.00 SPH 6/6 ADD O.U. PP 280/400
L.E. 1.00 SPH 6/6 -1.5 SPHPP 280/400
V PP—PO—PR / 400
EXERCISE FOR ACCOMMODATION. DIRECTIONS: HOLD THE SMALLEST PRINT YOU CAN READ 14 INCHES FROM YOUR EYES. BRING THE PRINT UP TO THE RIGHT EYE AND LEFT EYE SEPARATELY, AND THEN BOTH EYES UNTIL BLURRING OCCURS. REPEAT EACH PROCEDURE TIMES AT EACH EXERCISE PERIOD. WEAR READING DISTANCE NO LENSES.
Developed with grant from Markle Foundation.
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CONRAD BERENS, M. D.
GERALD FONDA, M. D.

Fig. 1.—Accommodation card used for home prism exercises while accommodating.

reduced and often dispensed with. In cases where a gradual reduction in the hyperopic correction is advised, minus spheres of increasing strength in clip-on frames may be worn. This method of assisting the patient to accept an increasingly weaker hyperopic correction may be continued until the patient maintains comfortable fusion on small print without the plus correction, or with his minimum correction when indicated. At this point, base-in prisms in clip-on frames are sometimes prescribed for short periods of reading or as an exercise while exercising supravergence (Fig. 3).

Diverging exercises while accommodating should be done daily at first. If the exercises have never been done previously, the patient is advised to begin cautiously. In general, 5 minutes once or twice daily are recommended in the beginning; the period is increased to 10 or 15 minutes a day. The prism rack is held alternately before each

Fig. 2.—The patient is doing diverging exercises while accommodating (with and without glasses).

Fig. 3.—The patient, who is wearing base-in plastic prisms to stimulate divergence, is also using vertical prism bar with base down before the left eye to stimulate supravergence against a low degree of high hyperphoria.

eye for approximately half the time allotted to the exercise period.

Converging exercises while accommodating may be performed in a manner similar to that described above, holding the prism rack with the smooth side next to the face and the base directed temporally. Normal retinal correspondence is a prerequisite for these exercises.

The following case reports illustrate the method of using this orthoptic technique and the results obtained.

CASE 1.—A boy, aged 12 years. First examined in November, 1952. He has no subjective complaints but is a slow reader. He was wearing the following correction: O. D. -0.75 sph $\bigcirc$ -0.37 cyl, ax $15=20/20$; O. S. -1.75 sph $\bigcirc$ 0.37 cyl, ax $15=20/20$. Screen and parallax with correction: esophoria 6Δ at 6 meters, esotropia 16Δ at 25 cm., when fixating on a 3 mm. white-headed pin. Ophthalmographic record with his correction revealed slight overconvergence when fixating first words in each line of reading; fixations and regressions markedly increased; number of words read per minute 54 below average (Grade 7 material). Comprehension of material read 100%.

Treatment.—Bifocal addition +2.00 O. U. which reduced the esotropia to esophoria 6Δ. Diverging exercises on major amblyoscope supplemented by diverging exercises with accommodation at home.

Jan. 24, 1953. Fused 400 mm. print through bifocal segment.

Feb. 21, 1953. Fused 300 mm. print through bifocal segment.

March 14, 1953. Fused 300 mm. print through upper segment.

April 25, 1953. Screen and parallax with distant glasses: orthophoria at 6 meters, esophoria 2Δ at 25 cm. while fixating on 300 mm. print. Without his myopic correction: orthophoria 6 meters, exophoria 4Δ at 25 cm. Prism divergence 4Δ at 6 meters, 8Δ at 25 cm. Bifocal segment was removed.

June 11, 1954. Ophthalmographic record is shown in the Table.

Ophthalmographic Records

	Speed, Words/ Min.	Fixations/ 100 Words	Regressions/ 100 Words	Comprehension, %
Case 1				
High school Av.	260	89-93	13-17	--
Patient				
Without prescription	334	56	4	90
With prescription (myopic corr.)	214	88	22	90
Case 2				
Second grade av.	147	147	45	--
Patient				
With prescription	231	104	32	90
Without prescription	107	136	48	100

Comment.—The patient reads normally and correctly without glasses. When reading with his myopic correction, the patient still overconverges at times and the number of words read per minute is markedly reduced (334 to 214).

CASE 2.—A boy was first examined in 1948 at the age of 4 years. Glasses were prescribed as follows: O. D. +2.25 sph $\bigcirc$ +0.25 cyl, ax $120=20/25$; O. S. +1.75 sph $\bigcirc$ +0.50 cyl, ax $120=20/20$. Screen and parallax with glasses: esotropia 40Δ at 6 meters, esotropia 50Δ at 25 cm. Orthoptic training was employed until the child had second-grade fusion on the major amblyoscope.

January, 1949. Operation: bilateral retroplacement[5] of the medial recti 3.5 mm. Fusion training was continued for a period of one and one-half years.

October, 1951. Screen and parallax with glasses: orthophoria at 6 meters and 25 cm. on 3 mm. white-headed pin. Without glasses: orthophoria at 6 meters, esophoria of 4Δ at 25 cm. Prism divergence with glasses: 12Δ at 6 meters, at 25 cm. 14Δ on 3 mm. white-headed pin.

The ophthalmograph record is given in the Table.

The patient overconverges less with glasses at the beginning of each line than without glasses. Although the child is in the second grade, the graph reveals excellent third-grade skills.

February, 1953. Screen and parallax with and without glasses: orthophoria at 6 meters, esophoria 6Δ at 25 cm. on 3 mm. white-

headed pin; esotropia 8Δ on 300 mm. print with glasses. Glasses are worn for near work; patient is given prism diverging exercises with accommodation at home.

May, 1954. Wearing reduced correction: O. D. +1.50 sph ⌒ −0.75 cyl, ax 170= 20/20. O. S. +1.50 sph ⌒ −0.75 cyl, ax 15=20/20. Screen and parallax with glasses: orthophoria at 6 meters and at 25 cm. on 300 mm. print; esophoria 4Δ reading 300 mm. print without glasses.

Comment.—This excellent functional result is attributed to the fine cooperation of an intelligent young patient and his parents.

Summary and Conclusion

A diverging exercise while accommodating is described, using an accommodation card, a prism rack, and, when indicated, plus and minus plastic spheres and/or prisms in clip-on frames.

This exercise is beneficial to many patients who are able to maintain fusion at 25 cm. on a 3 mm. white-headed pin or light but are unable to maintain fusion on small print, especially when reading.

Two case histories are cited. These patients showed marked improvement in their muscle balance and in their ability to fuse while reading, as revealed by classroom work and ophthalmographic records after the exercises were faithfully carried out. The fact that these exercises may be performed at home with inexpensive equipment adds to its practical value.

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Chiasmal Optic Neuritis

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Inflammatory affections of the optic chiasm are probably more frequent than existing records show. According to Duke-Elder,[1] they are seldom recognized.

Chiasmal optic neuritis is merely a variant of the well-known condition retrobulbar neuritis. The age and sex incidence of the former corresponds to that of the ordinary case of retrobulbar neuritis, as do its onset and course. The onset is sudden and is sometimes accompanied by headache and sickness and occasionally by visual hallucinations.

The visual field findings are bilateral, but these are frequently more pronounced in one eye than in the other.

The inflammatory foci in the optic tract may appear and subside. A retrobulbar lesion may often complicate the picture, and cases have been recorded in which the inflammatory process has extended to the optic nerve head, thereby producing a typical papillitis.

The pathology of this condition is similar to that of acute retrobulbar neuritis. Traquair[2] believes that most of these lesions are manifestations of multiple sclerosis. The bitemporal hemianopic visual field defects encountered in these cases indicate that this lesion is unquestionably chiasmal in location.

The visual field examination reveals rather pronounced central defects and relatively little disturbance in the periphery. The field defects may be irregular, and the scotoma in one or the other eye or in both eyes may be quadrantic in shape. These scotomata, as pointed out by Rönne,[3] show a tendency to fluctuate in size and to jump from one part of the field to another. Although the typical visual field defect is usually bitemporal, variations may and do occur. A small lesion, centrally located in the optic nerve, may produce an altitudinal defect, whereas a localized patch at the junction of one nerve with the optic chiasm may give rise to a hemianopic scotoma in the homolateral eye while the field in the other eye is normal. To this defect Traquair[2] has given the name "junction scotoma." It is logical to assume that if the involvement of the visual fibers in one optic nerve is extensive or complete there will be an extensive field defect or total blindness in the eye corresponding to the involved nerve.

The differential diagnosis of acute chiasmal neuritis includes conditions in which pressure upon the nerve causes interference with conduction, such as occur with a tumor or in chiasmal arachnoiditis, and vascular lesions. A tumor in this area and chiasmal arachnoiditis are characterized by a slow onset and a gradual increase in severity of symptoms, with no tendency to recovery. Vascular lesions in this area occur in elderly persons with signs of general arterial disease. In this latter group of patients the visual field defect appears suddenly and is unilateral and either stationary or progressive. In these, too, sector defects are commoner than a central scotoma.

As in acute retrobulbar neuritis, the immediate prognosis insofar as vision is concerned is, generally speaking, good.

The field changes disappear with or without treatment more or less completely. It is a generally accepted dictum that the prognosis is worse the longer the onset of improvement is delayed. Chronic conditions usually show greater visual defects than acute cases.

The treatment of this disorder is the same as that of acute retrobulbar neuritis. The

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therapy should be directed against the cause. Typhoid vaccine administered intravenously may abort the attack, according to Benedict.[4] The induction of vasodilatation by sodium nitrite intravenously has been advocated by Duggan.[5] Lately, histamine by continuous saline infusion has been recommended. Here again, as in conditions where nervous tissue is involved to any degree, the liberal use of thiamine hydrochloride is indicated.

Report of a Case

A 22-year-old white man was first seen by me on Nov. 3, 1949, with the history of sudden loss of straight-ahead vision in the right eye two and a half months prior to his admission to the hospital. There was no history of disease or trauma at that time. However, the patient stated that about one month prior to the onset of his loss of vision he and a friend motorcycled to California and back to Richmond, Va. The patient did all the driving and admitted drinking rather heavily throughout the trip.

The general physical examination of the patient was negative except for carious teeth.

The examination of the eyes was as follows:

Vision: O. D. 20/25−1, J 1; O. S., finger counting at 2 ft.

Pupils: O. U., round, equal, reacted to light and in accommodation directly and consensually

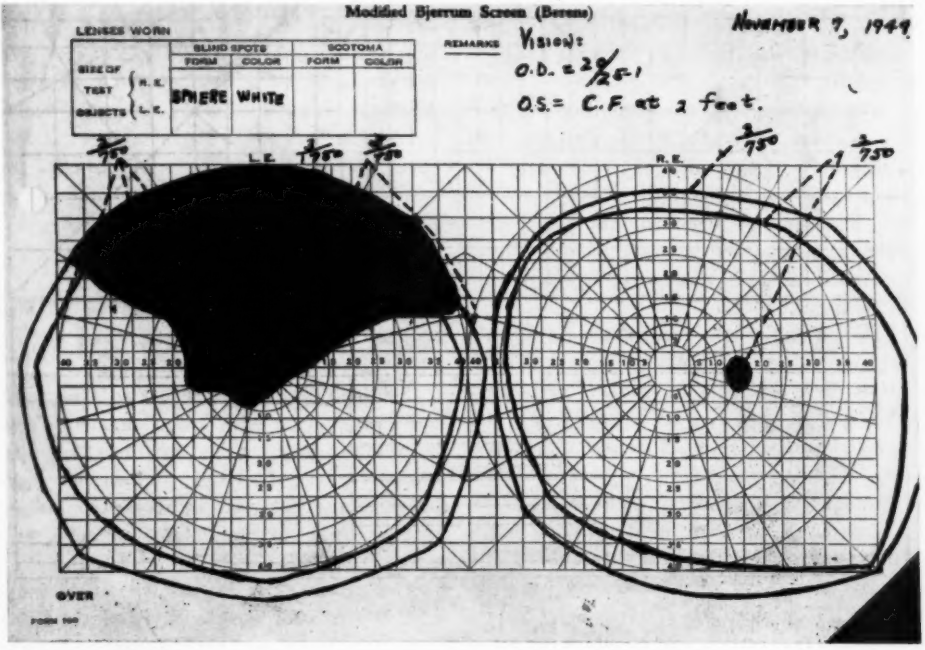
Muscle balance and media: O. U., normal

Fundi: O. D., within normal limits; O. S., equivocal pallor of the temporal portion of the disc

Visual fields: O. D., normal; O. S., an almost complete superior altitudinal hemianopsia enveloping fixation between 5 and 10 degrees inferiorly (Fig. 1).

The laboratory data, including spinal fluid examination, were well within normal limits. Roentgenological examination of the paranasal sinuses revealed a slight cloudiness in the left frontal sinus and a moderate amount of cloudiness in the ethmoids. Roentgenological

Fig. 1.—Visual fields on admission.



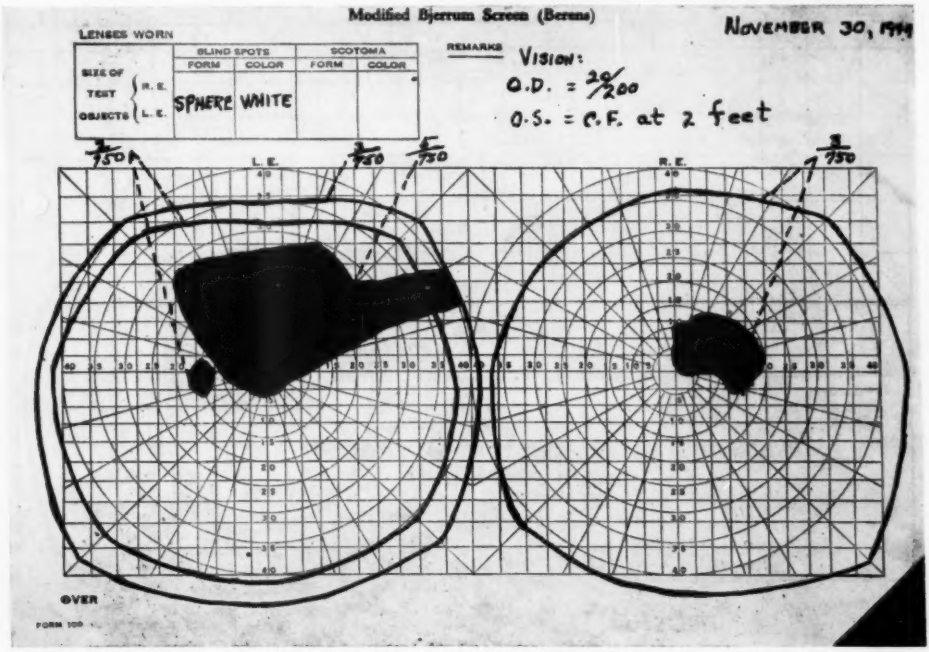
examination of the skull, including special views of the sella turcica and optic foramina, showed no evidence of abnormality.

Consultations with the medical and genitourinary services did not disclose any foci of infection. Consultation with the ear, nose, and throat service revealed a chronic tonsillitis.

Course in the hospital: with the presumptive diagnosis of acute retrobulbar neuritis, the patient was given 300,000 units of penicillin daily for 10 days. This was followed by five intravenous injections of typhoid vaccine (an injection given every other day), followed by massive infusions of typhoid vaccine for two additional treatments. Three carious molars were extracted. No improvement was noted in the affected eye after all the preceding treatment. Then, on Nov. 30, 1949, the patient noticed sudden loss of vision in the good eye, that is, the right one. The vision of this eye was immediately checked and was found to be 20/200, from a visual acuity of 20/25−1 on admission. A visual field study of both eyes was done on the same day, and a quadrantic type of scotoma was found in the right eye (Fig. 2). The visual field defect of the left eye was similar to the one obtained on admission, but it was definitely smaller and there was a definite area of vision between the periphery of the scotoma and the limits of the visual field for that eye. It was thought that these findings were suggestive of an inflammatory involvement of the anterior portion of the optic chiasm.

At this stage I also considered the possibilities that I might have been dealing with a case of opticochiasmatic arachnoiditis or of Cushing's syndrome of the optic chiasm. For these reasons and in view of the fact that the patient's vision did not show any signs of improvement and, on the contrary, had continued to deteriorate, I ordered both a neurological and a neurosurgical consultation. The neurological examination was negative except for an absent right abdominal reflex. The neurosurgical study, which included a

Fig. 2.—Visual fields at onset of loss of vision of the right eye 27 days after the onset of loss of vision in the left.



cerebral arteriogram and a pneumoencephalogram, did not shed any light on the case. Furthermore, according to the neurosurgeons, there was nothing to suggest the presence of arachnoiditis in the region of the optic chiasm. The neurosurgeons, however, believed that, in view of the fact of the patient's marked visual loss and the fact that some time had gone by, a chiasmal exploration was in order. This was carried out, and the optic nerves and chiasmal region revealed no abnormality.

Examination of the patient's fundi on Feb. 12, 1950, showed rather definite temporal pallor of the optic nerve heads of both eyes. The visual acuity had decreased to finger counting at 3 ft. in the right eye and to finger counting at 2 ft. in the left.

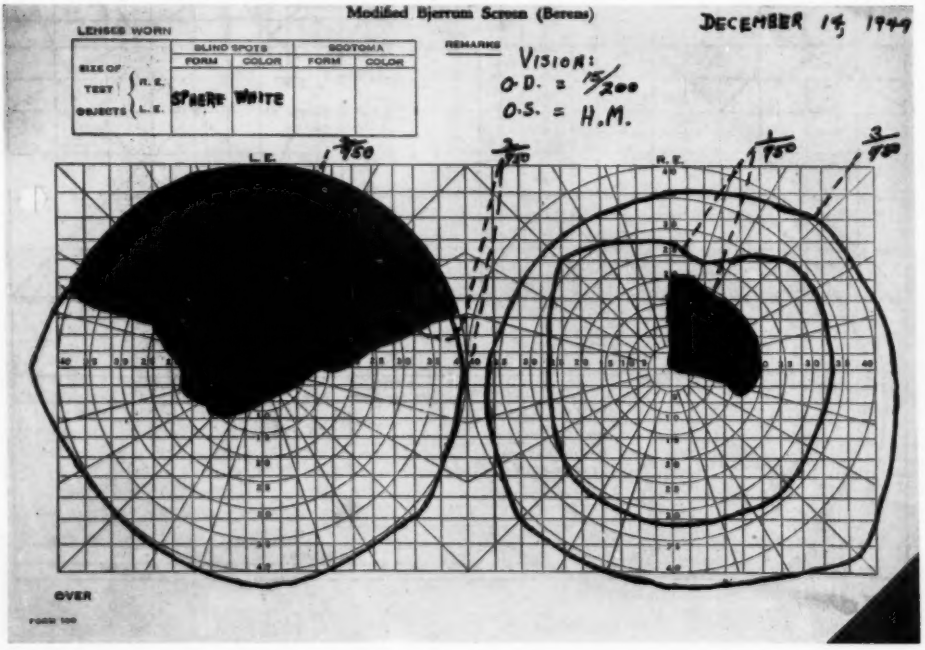
In view of the preceding, the only possible diagnosis in this case was that of acute chiasmal neuritis.

Comment

The present case has been considered worthy of publication for several reasons. First of all, these cases are apparently rarely recognized, probably because ophthalmologists do not take pains to determine visual fields accurately. It is therefore pertinent to call to the attention of oculists in general that such lesions exist and that they should be searched for. Secondly, this case showed the characteristic behavior followed by cases of chiasmal optic neuritis as pointed out by Traquair. For instance, it showed the fluctuating nature of these lesions. This fact can be appreciated by comparing the visual field of the left eye, determined on Nov. 7, 1949, with that determined on Nov. 30, 1949, and the latter with that determined on Dec. 14, 1949 (Fig. 3). This case also shows the difficulties encountered in trying to establish an etiologic diagnosis. The rare feature of an altitudinal hemianopsia was also shown by the present case.

In spite of vigorous treatment this patient showed no improvement insofar as his visual acuity was concerned, and five months after admission it was unchanged. Optic atrophy set in, in both eyes.

Fig. 3.—Visual fields five weeks after admission. Comparison of these visual fields with the two previous ones shows the fluctuating nature of the lesion.



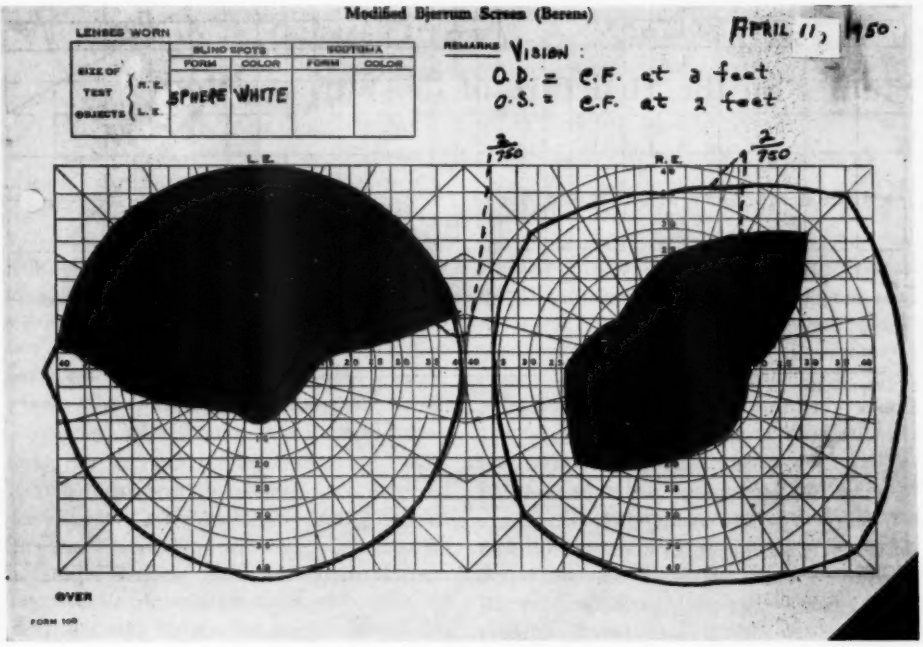


Fig. 4.—Visual fields five months after onset of the disease.

Unlike the course in most cases of retrobulbar neuritis, the vision did not return, the case following the precept mentioned by Traquair that the prognosis for vision is worse the longer the onset of improvement is delayed. In this case there was at no time any sign of improvement in visual acuity, and the patient appeared doomed so far as sight was concerned, as five months after admission there were definite signs of bilateral optic atrophy in the temporal portions of both nerves.

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Studies on the Structure of the Vitreous Body

III. Cells in the Cortical Layer

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The cellular components of the vitreous body have been subject to some controversy. It has been established that in the course of embryonic development the vitreous body contains numerous cells, but their nature and origin are not well known. The adult vitreous body is considered to be primarily cell-free. However, in the cortical layer, the so-called "hyaloid area," different types of cells have been described repeatedly.

One of the first reports on the cells in the adult vitreous body is that of Henle (1841), who mentions "cytoblasts" in the vicinity of the zonula fibers. Donders (1847) studied the posterior surface of the vitreous body and described "corpuscles," which Doncan (1854) later characterized as cells. Doncan gives a detailed description of these cells in the cortical layer of the human vitreous body as well as in the vitreous body of cattle, dogs, cats, rabbits, and several kinds of fish. His illustrations show the presence of granular protoplasm and filamentous processes, and he suggests that the function of these cells is to produce the vitreous body (*corpus vitreum metamorphosi cellularum colloidea nascitur*). This assumption might originate from Virchow (1852), who first described the cells in the embryonal vitreous body, which he characterized as a mucoid tissue (*Schleimgewebe*). In contrast to these findings, Brücke (1847), Finkbeiner (1855), and Ritter (1865) described a continuous sheet of epithelial cells on the posterior surface of the vitreous body.

Further studies of the cells in the adult vitreous body were made by Klebs (1860), Weber (1860), and Iwanoff (1865). Iwanoff observed these cells not only in fixed and stained preparations but also in supravital samples. He distinguished three different cell types: round cells with granular protoplasm, cells of irregular shape with filaments, and cells characterized by large vacuoles within the protoplasm. He speculated that the filamentous cells produce the fibrils of the vitreous, while the granular and vacuolar cells are responsible for the formation of the "mucoid" material. Iwanoff's excellent and detailed description of these cells resulted in the general acceptance of their presence as a regular constituent of the vitreous body, and they were described in detail in the textbooks of the second half of the last century (Henle, 1866; Kölliker, 1867; Stricker, 1872).

Some doubt as to the regular occurrence of these cells arose after Schwalbe (1874, 1887) and Potiechin (1878) suggested that they are macrophages. According to this theory, their occurrence in the vitreous body was incidental and their morphological structure was considered to be similar to that of leukocytes or lymphocytes. This conclusion was based partly on morphological interpretation of the cellular structure and partly on experimental work. It was shown by Schwalbe (1874) and confirmed

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by Potiechin (1878) that implants of the cell-free vitreous gel into the dorsal lymph sack of the frog become populated by lymphocytes closely resembling the cells of the vitreous body. According to Potiechin (1878), the introduction of foreign material into the vitreous body also leads to a large accumulation of similar cells.

An unsuccessful attempt to demonstrate neuroglia-type cells in the cortical layer of the adult vitreous body was made by Contino (1923), who found cell-like formations ("astrocytes") in the vitreous body after sublimate fixation and silver impregnation. Later Greeff (1927) demonstrated on albumin and gelatin models that these astrocytes are artifacts. López Enríquez (1931), who studied the cells at the periphery of the vitreous body in a case of glaucoma, suggested that they originate from the microglia (Hortega) cells of the retina and supported this assumption by morphological observations of cells in tissue cultures of neuroglia.

In the decades which followed, interest in these cells decreased considerably. In a detailed review of the development of the vitreous body in different species, Jokl (1927) discussed the properties of these cells. Redslob (1932) described them as noncellular formations connecting the vitreous body with the retina. Weve (1934) recognized the cellular character of these formations and emphasized their importance as connecting structure between the retina and the vitreous. More recently, Schwarz and Schuchardt (1950) observed cells in the cattle vitreous body, but no cytological details were reported. While this investigation was in progress, we became aware of a concurrent study by Hamburg (1957) on the distribution of these cells in various animals and their phagocytic character.

The investigations reported in this paper were initiated after we had observed these cells while studying the chemical composition of the cortical layer of the vitreous body (Balazs, 1954). Because of the possibility that these cells might be of some significance in the metabolism of the vitreous body, more detailed cytological and histochemical investigations seemed imperative.

Material and Methods

This report is based on a study of 108 eyes from Aberdeen-Angus and Haffner steers and cows (approximately 2 years of age) obtained from the slaughterhouse within 30 to 45 minutes after the animals had been killed. Studies on the eyes of 18 rabbits (1 to 2 years of age), 10 rats (2 to 6 months of age), 4 roosters (approximately 1 year old), and 7 humans (varying from 19 to 73 years of age) * are also included. The eyes of the laboratory animals were used immediately after the animal had been killed. The human eyes were obtained after a postmortem period of 1½ to 24 hours. The eyes were dissected by carefully removing the sclera and the retina posterior to the ora serrata. In the steer eye the separation of the retina from the vitreous body caused no difficulty; in the other species, however, the adhesion of the two tissues was stronger. Small portions of the cortical layer were then obtained from the exposed free surface of the vitreous body and were studied immediately, by phase-contrast microscopy, or after fixation and staining.

A. Phase-Contrast Microscopy.—Small pieces of the cortical layer were placed on slides and, with or without the addition of a small drop of a physiological balanced salt solution, were covered and sealed with paraffin. Two types of physiological balanced salt solution were used; one (pH 7.2 to 7.4) was described by Earl (1943), and the other (pH 7.0), by Simms (1942). Both buffered salt solutions at times contained 0.002% to 0.01% phenol red as pH indicator. The preparation was kept

* Six human eyes were obtained from the Boston Eye Bank. These eyes were considered to be normal, since the cause of death was unrelated to the condition of the eyes. One eye, obtained through the courtesy of Dr. Robert J. Brockhurst, was enucleated for a choroidal melanoma; only the normal lateral portions of the vitreous body of this eye were used.

at 37 C while it was studied with a Leitz phase-contrast microscope. For the most part, a 90× oil-immersion objective was used, and photographic records were made with a Leica camera attachment. In order to study the cellular changes after fixation and supravital staining, the preparations were sealed along two edges only and perfusion under the cover glass was effected through the use of filter paper strips. In this way, it was possible to follow the changes of the same cell from the living state through the process of fixation and staining.

B. Fixed Preparations of the Vitreous Surface.—In order to obtain permanent preparations the following method was used: The retina was removed, and the fixing fluid was poured onto the free surface of the vitreous body. Small pieces were cut out of the cortical part of the vitreous and immediately immersed in the fixing fluid. Following fixation, staining was carried out on these pieces.

C. Sections of the Vitreous Body and the Retina.—The cortical part of the vitreous body, with the adhering retina and sclera, was immersed in the fixing fluid. The fixed material was cut into smaller pieces, dehydrated in ethyl alcohol, and embedded in paraffin after treatment with cedarwood oil and xylene. Embedding in gelatin was carried out according to the Gaskell-Gräff method (Romeis, 1948).

The following fixing fluids were tested: 2% osmic acid (OsO_4) dissolved in 0.1% chromic acid and applied both as a liquid fixative and in vapor; Flemming's fluid; Palade's (1952) buffered osmic acid (barbital [Veronal] buffer, pH 7.3 to 7.4); 2% osmic acid dissolved in balanced salt solution (Simms or Earl); alcoholic formalin (40% formaldehyde and 95% ethyl alcohol, 1:9); 2% or 4% formalin in pH 7.4 barbital buffer or in balanced salt solution (Simms or Earl); 4% formalin with 1% calcium chloride added; 4% basic lead acetate; absolute methyl alcohol; Bouin, Zenker, and Kolmer's fluid.

Staining was carried out with Harris' hematoxylin and eosin or Heidenhain's iron hematoxylin. For the study of basophilia and metachromasia, 2×10^{-4} M azure A† and 5×10^{-3} M toluidine blue,† both dissolved in distilled water, were used. For lipid staining colloidal Sudan III † and Sudan black † were used according to the method described by Romeis (1948). Staining with Nile blue ‡ was performed according to Pearse (1954). The periodic acid-Schiff (PAS) reaction was applied according to the method described by Lillie (1954); however, potassium bisulfite was used instead of sodium bisulfite, and, in some cases, oxidation with periodic acid was prolonged to two hours. The peracetic acid-Schiff (PAAS) reaction was carried out according to Pearse (1954).

The preparations were mounted in glycerin, Paragon mounting medium, or Canada balsam. The preparations stained with azure A or toluidine blue were mounted in water or, after dehydration in methylbenzoate, in Canada balsam.

In an attempt to determine the nature of the basophilic and PAS-positive granules, digestion with animal diastase,§ human saliva, and testis hyaluronidase ‖ was carried out. Hyaluronidase, 150 to 1000 U. S. P. (turbidimetric) units, or diastase, 5 to 50 mg. was dissolved in 20 ml. pH 7.4 balanced salt solution (Earl) or in 20 ml. 1/15 M pH 7.0 phosphate buffer. The human saliva was diluted with an equal volume of balanced salt solution (Earl). Samples of the cortical layer of the vitreous body were placed in the solution and incubated for two to four hours at 37 C with constant slow shaking. Samples were incubated with the above-mentioned enzyme solutions prior to and after fixation in Palade's buffered osmic

† Obtained from the National Aniline Division of the Allied Chemical and Dye Corporation, New York 6.

‡ Obtained from the Matheson Company, East Rutherford, N. J.

§ Obtained from the Nutritional Biochemical Corporation, Cleveland.

‖ Wydase, obtained from the Wyeth Laboratories, Inc., Philadelphia.

Fig. 1.—Cells in the cortical layer of the cow vitreous body. Fresh preparation in phase contrast; reduced about 11% from mag. × 237.

acid or in 2% formalin in Earl's balanced salt solution. Following incubation the unfixed samples were fixed in buffered osmic acid and stained with the PAS technique.

Results

1. *Phase-Contrast Microscopy of Fresh Preparations.*—Supravital preparations of the cortical layer, observed under low power, reveal a large number of cells covering the surface of the vitreous body (Fig. 1). They are scattered irregularly throughout the whole surface of the cortical layer and seem to be embedded in the superficial part of the vitreous gel. By moving the cover glass of such a preparation, one can observe that these cells do not move freely, but follow the displacement of the gel. Under high power the cells always appear spherical, provided that pressure from the cover glass is prevented by interposition of hair or another cover glass. The shape of these cells makes it difficult to distinguish intracellular details under phase-contrast microscopy (Fig. 2). However, when the cells become flattened by the pressure of the cover glass vacuoles, granules, and protoplasmic filaments are clearly distinguishable (Fig. 3). The granules, which are somewhat smaller (0.5μ to 2μ) than the vacuoles, are localized mainly around the nucleus (Fig. 4). Although the nucleus is sometimes ovoid, for the most part it is kidney-shaped or lobular, containing one or two nucleoli. It was found that these cells are able to survive under these conditions for a

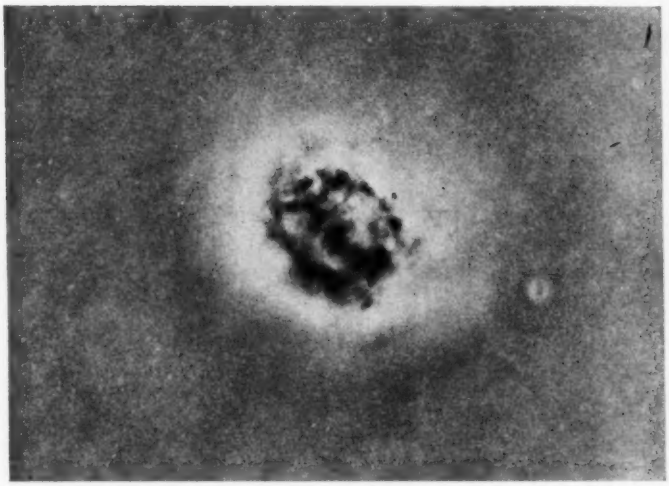

Fig. 2.—Cell in the cortical layer of the steer vitreous body. Fresh preparation in phase contrast; oil immersion; reduced about 11% from mag. × 1296.

limited time, during which slow movement of the granules and the cell surface can be observed. In preparations which are not fresh or have been kept under the microscope for a prolonged time, the sharp outlines of the protoplasm disappear and the nuclear membrane and chromatin structure become visible (Fig. 5). In the further course of postmortem degeneration, the slow movement of the granules ceases, small protoplasmic particles show vivid Brownian movement, an extreme prolongation of the protoplasmic filaments occurs, vacuolization and lysis of the protoplasm takes place, and the nuclei show swelling or karyorrhexis resulting in the appearance of extremely lobular or double nuclei.

The cells described were observed in all species studied, and their general morphological appearance was found to be similar. Their size is somewhat smaller in the rat and in the rooster. The number of

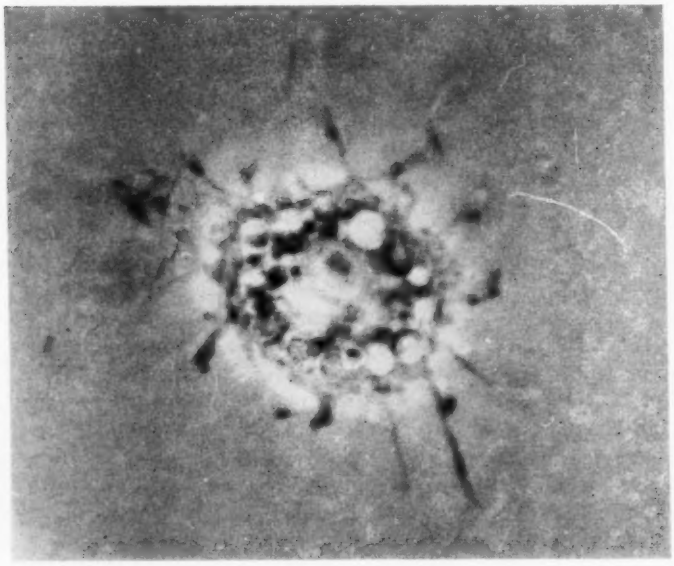

Fig. 3.—Cell in the cortical layer of the steer vitreous body. Fresh preparation in phase contrast; oil immersion; reduced about 11% from mag. × 1296. Granular and vascular structure and protoplasmic filaments shown after the cell flattens out.

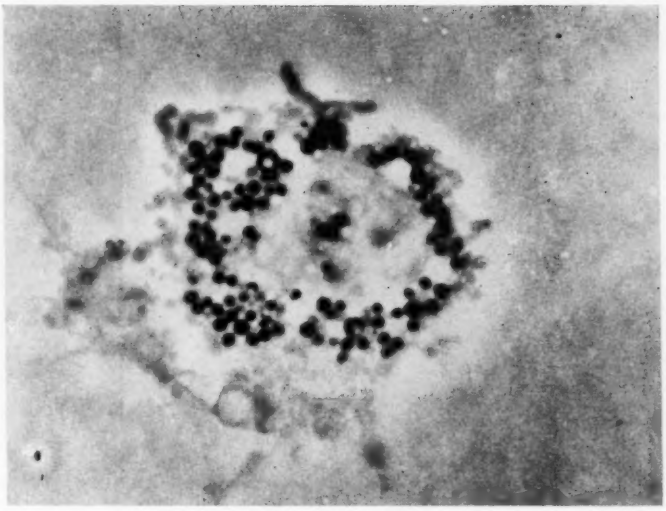

Fig. 4.—Cell containing numerous granules (same preparation as Fig. 2). The flattening of the cell may be due to pressure from the cover glass. Phase contrast; oil immersion; reduced about 11% from mag. × 1296.

granules shows considerable variation within the same species. Although no quantitative studies were performed to determine the number of granules per cell, one can state that the smallest number of granules among the species studied was found in the rooster eye, and the cells of the rabbit eye contained a slightly larger number of granules. The largest number of granules was found in the cells of cattle and human eyes.

2. *Supravital Reactions to Fixation and Staining.*—In order to compare the appearance of these cells in fresh preparations with their morphology in fixed and stained preparations, we followed the fixation and staining processes under the phase-contrast microscope. Unbuffered osmic acid and Bouin's fluid did not preserve the granules and vacuoles; with both fixatives they disappeared within 10 minutes after perfusion

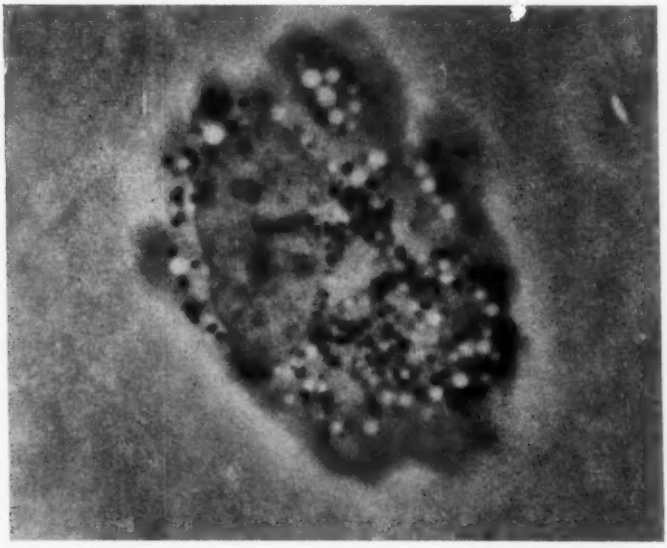

Fig. 5.—Cell from the cortical layer of the human vitreous body, 42-year-old woman. Death due to bronchopneumonia. Photomicrograph was taken six hours after death and one and one-half hours after enucleation. Fresh preparation in phase contrast; oil immersion; reduced about 11% from mag. × 1296.

Fig. 6.—Cell from the cortical layer of the cow vitreous body. *A*, fresh preparation in phase contrast; oil immersion; reduced about 32% from mag. × 1296. *B*, same cell following perfusion of the preparation under the microscope first with buffered osmic acid, then with Sudan III in 70% ethyl alcohol, and finally with azure A in distilled water. Picture *B* was taken in bright field 165 minutes after Picture *A*. The granules shown in phase contrast (*A*) stain slightly with Sudan III and strongly with azure A (*B*). Diffuse blue-violet staining of the protoplasm, metachromatic staining of the nucleus, and unstained vacuoles could be observed in *B*.

had started. A small part of the granules was preserved with 4% formalin, but swelling and bubble formation could be observed in the protoplasm. Other fixatives without buffer also proved unsatisfactory. The best preservation of cytological details was achieved with buffered osmic acid. The use of 4% formalin in barbital buffer or in balanced salt solutions was somewhat less successful. Even with the best fixation, retraction of the cytoplasmic processes and some changes in the vacuoles could be observed. Despite this, the general morphological structure is well preserved in the course of this type of fixation and subsequent staining procedures. Figure 6 shows the same cell in phase contrast prior to fixation (*A*) and after buffered osmic acid fixation and staining with azure A (*B*). The vacuoles and granules remain unchanged during

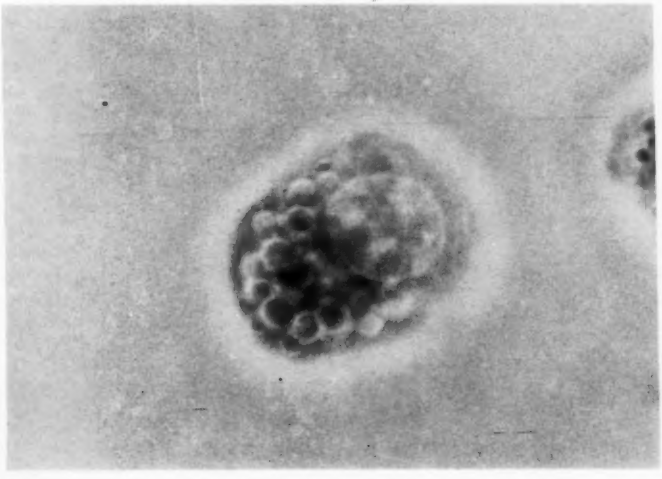

Fig. 7.—Cell of the steer vitreous body. Fresh preparation suspended in buffered salt solution (Simms) containing 0.0001% neutral red; phase contrast; oil immersion; reduced about 11% from mag. × 1296. Slightly swollen granules are stained by neutral red.

fixation. The vacuoles show no staining, while the granules show distinct orthochromatic staining with azure A.

In another experiment the supravital uptake of neutral red was studied. This was accomplished under the microscope by perfusion of the sample with balanced salt solution containing 0.0001% neutral red. Rapid entrance of the stain into the cytoplasm was observed. Most of the stain was taken up by the granules, which showed marked swelling (Fig. 7). In cells which showed signs of decreased vitality, such as a marked nuclear membrane or precipitation in the nuclei, the granules did not take up dye but the nucleus showed diffuse staining.

3. *Fixation of in Toto Preparations of the Cortical Layer.*—Small parts of the cortical gel were treated with osmium vapors by placing them in a closed vessel containing a few drops of 2% osmic acid and were subsequently stained with azure A. This procedure was found to be satisfactory for demonstrating hyaluronic acid in the chicken comb (Szirmai, 1956); viz., while the osmic acid vapors preserved the proteins and lipids, the azure A precipitated the hyaluronic acid, forming a metachromatic complex. In the cortical layer of the vitreous body, the extracellular hyaluronic acid was precipitated by azure A, forming metachromatic granules. The massive granular precipitate masked the cellular details. The presence of this metachromatic precipitate in the vicinity of the cell made it extremely difficult to distinguish between extracellular and intracellular granules. In order to precipitate the easily soluble mucopolysaccharides, 4% basic lead acetate was also used. Subsequent azure A staining showed extracellular metachromatic precipitate and orthochromatic granules in the cells.

The liquid fixatives which best preserved the cytological details without retaining the extracellular hyaluronic acid were buffered osmic acid and buffered formalin. If unbuffered osmic acid or formalin was used or if these fixatives were not isotonic,

Fig. 8.—Cells in the cortical layer of the cow vitreous body. Preparation suspended for 45 minutes in 2% buffered osmic acid (Palade), then washed and mounted in distilled water; bright field; reduced about 11% from mag. × 575. The granules are blackened by osmic acid.

swelling and subsequent confluence of the granules could be observed. The uptake of osmium by the cells was evidenced by the marked blackening of the granules (Fig. 8). When 0.01% neutral red was added to the buffered formalin solution, the granules showed a distinct orange-red color and preservation of other cellular details was also good. When a concentration of 2×10^{-4} M azure A was added to the buffered osmic acid fixative, the granules clearly showed azure A uptake.

4. *Staining of in Toto Preparations of the Cortical Layer.*—Staining of the preparations of the cortical layer was performed after buffered osmic acid fixation. Staining with hematoxylin and eosin and with Heidenhain's iron hematoxylin resulted in slight swelling of the granules and some shrinkage of the nuclei. As a result of this shrinkage, the nuclei were more kidney-shaped or bilobular. The vacuoles remained unstained, and the granules showed a weak yellowish-gray color.

Staining with azure A or toluidine blue resulted in deep blue orthochromatic coloring of the cytoplasmic granules. There was diffuse blue-violet coloring of the protoplasm with the exception of the vacuoles, which remained practically unstained (Fig. 9). The nucleus stained metachromatic and retained its color during dehydration in methylbenzoate.

Staining with Sudan III gave a pale orange coloration to the granules. This was sometimes overshadowed by the effect of osmic acid, but it was more distinct after buffered formalin fixation. Some blackening was also obtained with Sudan black, although the staining was not very strong. A freshly made solution of Nile blue stained the granules violet and the nuclei blue; a solution which had not been freshly prepared stained the granules blue.

With the PAS technique the granules reacted strongly positive, with light reddish staining of the extracellular substance (Fig. 10). Varying the time of periodic acid oxidation from 15 to 120 minutes did not change the intensity of the red color of the granules. The PAAS reaction showed no coloration of the granules even after oxidation for three hours. When the PAS staining was repeated on this same material following the PAAS reaction, the granules still showed intense red staining.

5. *Distribution of Cells in the Surface Layer of the Vitreous Body.*—The sclera, choroid, and retina posterior to the ora serrata were completely removed from fresh steer eyes. Care was taken not to injure the surface of the vitreous gel. The free surface of the gel was immersed in buffered osmic acid solution containing 5×10^{-4} M azure A. After 12 hours of storage at +4 C the vitreous gel showed considerable hardening and the cells on the surface were easily visible under low-power magnification, owing to the accumulation of azure A in the intracellular granules. The volume of the vitreous gel did not change significantly during this process. The cells are evenly distributed along the entire surface of the vitreous with the exception of the area of the optic disk, where the continuity of the surface is interrupted, resulting in a cell-free area. There are approximately 50 to 100 cells per square millimeter. All the cells are located on the surface of the vitreous adjacent to the retina. No cells could be observed inside the gel or on the surface layers of the vitreous body next to the lens. The cells are evenly distributed throughout the surface; however, accumulations of cells in groups forming branching lines could be observed (Fig. 11). This suggests an increased cell population, which may correspond to ramifying retinal vessels. It should be emphasized that only a small part of the cell population participates in these distinct areas. This was observed in adult steer and cow eyes.

6. *Sections of the Vitreous Body and the Retina.*—It is conceivable that some of these cells remain attached to the inner surface of the retina during the separation of the retina from the vitreous body. Since phase-contrast studies of the retinal surface

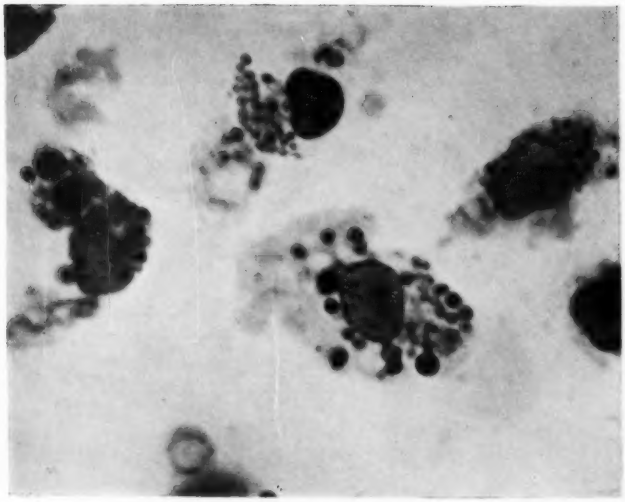

Fig. 9.—Cells of the cortical layer of the steer vitreous body. The granules are stained orthochromatically, and the nucleus is slightly metachromatic. Fixed in 2% buffered osmic acid (Palade); stained with azure A; mounted in distilled water; oil immersion; × 1089; Ektachrome.

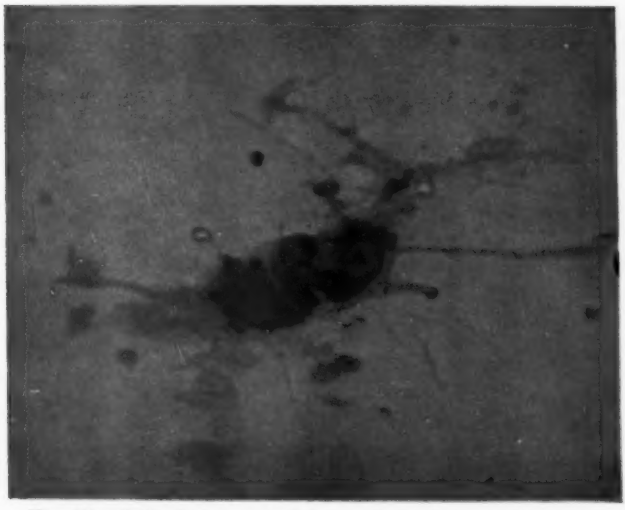

Fig. 10.—Cell of the cortical layer of the human vitreous body (same eye as in Fig. 5). The cell granules stain heavily with the PAS reaction. Fixed in buffered osmic acid; stained with PAS reaction, followed by nuclear staining with Harris' hematoxylin; mounted in Canada balsam; oil immersion; × 1089; Ektachrome.

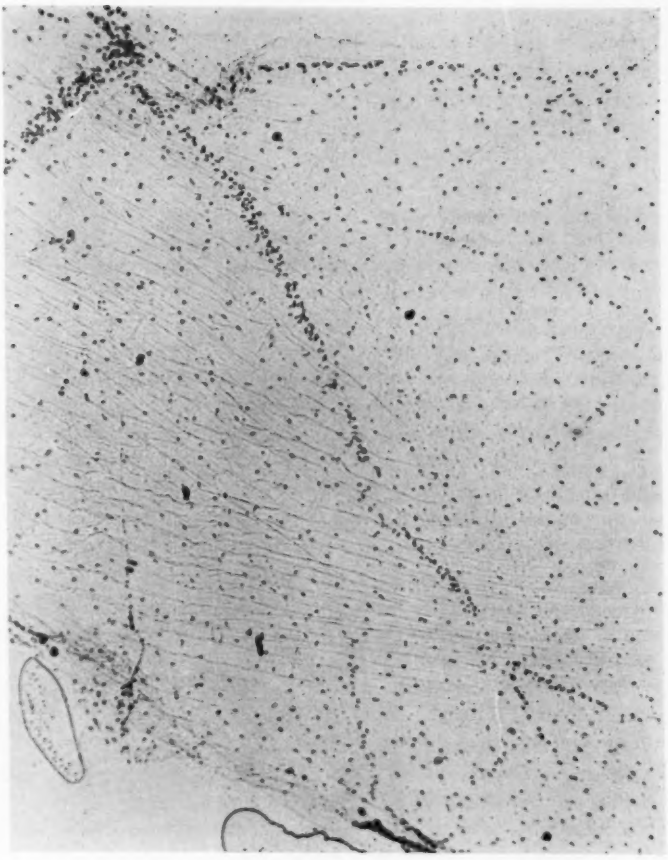

Fig. 11.—Distribution of cells in the cortical layer of the cow vitreous body. Preparation was fixed in buffered osmic acid, stained with azure A, and mounted in distilled water; reduced about 11% from mag. × 22. Some of the cells are distributed along branching lines.

did not clarify this point, sections of fixed and embedded samples were investigated. In these preparations, one could observe on the inner surface of the retina a number of cells similar to those located on the surface of the vitreous body (Fig. 12). Although their preservation is less satisfactory after embedding in paraffin, their morphology, especially the positive PAS reaction and the basophilia of the granules, makes it possible to identify them with the cells of the vitreous surface. This was possible only when buffered osmic acid was used as fixative. They were often found in close proximity to the retinal vessels but never in the layers of the retina.

7. *Enzyme Treatment of the Cells.*—Testis hyaluronidase, diastase, and human saliva did not change the PAS-positive reaction of the granules. The PAS reaction of the granules did not differ from the reaction of the cells which had been kept in buffered solutions without these enzymes for the same period of time and under the same conditions.

Comment

This study confirms the presence of cells in the cortical layer of the adult vitreous body. Their occurrence in the several species studied suggests that they are regular constituents of the vitreous body and that their presence is not incidental.

Despite some differences in the morphological description, the cells on which these studies are based are the same as

Fig. 12.—Microscopic section of part of the retina and the cortical layer of the vitreous body of the steer eye. It was fixed in Bouin's fluid, embedded in paraffin, sectioned, stained with Harris' hematoxylin and eosin, and mounted in Canada balsam; reduced about 11% from mag. × 144. The angle of this section was approximately 45 degrees to the surface of the vitreous body. Arrows indicate four cells in the cortical layer of the vitreous body. The granules of these cells disappeared, because of inadequate fixation.

those identified by Doncan (1854), Weber (1860), Iwanoff (1865), Potiechin (1878), Retzius (1894) and Bertacchini (1902). Presumably, they are the cells referred to as "hyaloideal cells" or "vitreous body cells" (*Glaskörperzellen*) in the textbooks of the last century (Henle, 1866; Kölliker, 1867; Stricker, 1872; Schwalbe, 1887, and others), and they are the same cells as those later observed by Cattaneo (1931), Weve (1934), and Hamburg (1957).

The physiological function of the cells of both adult and embryonal vitreous body has been subject to much speculation without adequate experimental support. In general, there have been two lines of thinking among investigators. According to one group, these cells produce the vitreous body or some of its components. According to the other, these cells are macrophages which participate in the defense mechanism of the hematoparenchymal barrier of this area. As to the first assumption, it should be emphasized that this was suggested only in reference to the formation of the vitreous body in embryos. This was first proposed by Virchow (1852) and has since been considered by several authors (Doncan, 1854; Iwanoff, 1865; Bertacchini, 1902; Magitot and Mawas, 1913). In the opinion of these investigators, certain morphological characteristics, such as the impressive number of granules or the vacuolization and peripheral fragmentation of the protoplasm, provide convincing evidence for the "secretory activity" of these cells. The second assumption, that these cells are part of a cell system the primary function of which is phago-

cytosis, was based on morphological considerations (Potiechin, 1878; Schwalbe, 1874, 1887). Their close relation to blood vessels was regarded by Ranvier (1892), Virchow (1900), Chrustschoff (1926), and Vonwiller and Kotlarewskaya (1932) as evidence for the macrophage character of these cells. The criterion for establishing the phagocyte character of a cell type and including it as part of the reticuloendothelial system is generally based on the ability of the cell to take up colloidal particles and vital stains after systemic administration. It became evident during the early studies that this does not apply to the vitreous cells. The studies of Rados (1913), Schnaudigel (1913) and Blotevogel (1924) suggest that vital staining of these cells after intravascular administration of the stain can be achieved only in newborn or very young animals. In adult animals, vital staining and phagocytosis can be observed only after the administration of very large doses or after injury to the eye, such as puncture of the anterior chamber (Schnaudigel, 1913; Hamburg, 1957). This is probably due to the development of the hemato-ocular barrier in the adult animal (Towbin, 1933; Wislocki and Ladman, 1955). Injection of colloidal material into the vitreous body results in phagocytosis, accompanied by an increase in the number of cells in the vitreous body as a result of cellular infiltration (Potiechin, 1878; Gray, 1933; Hamburg, 1957).

The observations reported in this paper offer little solution to the problem of the function of these cells in the cortical layer of the adult vitreous body. The basophilic granules with strong PAS positivity do not necessarily indicate the presence of carbohydrate components in the granules, but they certainly do not disprove this possibility. The strong PAS positivity of the granules after diastase and saliva treatment indicates that the granules do not contain glycogen, at least not in a form similar to that in other parenchymal cells, where treatment with these enzymes results in a disappearance of the PAS positivity. In this connection, it may be of interest to mention that Bembridge and Pirie (1951) observed PAS-positive extracellular granular material in the inner retinal layers of young rabbits. Their attempt to further identify this material was unsuccessful because of the easy solubility of the granules. Serpell (1954) described PAS-positive granules in the inner retinal layers during early stages of retrolental fibroplasia and assumed that the granules contained glycogen. The fact that testis hyaluronidase does not remove the granules indicates one of two things: Either the granules are not the storage place for hyaluronic acid or chondroitin sulfuric acid or, if these two mucopolysaccharides are stored there, they are stored in a form which is not accessible to this enzyme.

One of the most interesting aspects of the localization of these cells is their relation to the extracellular hyaluronic acid content of the vitreous gel. One of us (Balazs) reported in 1954 that the hyaluronic acid concentration in the cattle eye decreases gradually from the cortical layer toward the center of the vitreous body to the posterior surface of the lens. In adult steers it was found that the hyaluronic acid concentration in the cortical layer of the vitreous body, where these cells are located, is approximately 0.2 mg. per 100 cc. This is 5 to 10 times higher than that of the central-anterior region of the vitreous body. These cells are "embedded" in the collagen gel containing the highest known concentration of hyaluronic acid in normal adult mammalian tissues. The morphological uniformity of these cells, their regular distribution along the retina, and their localization in the surface layer of the vitreous containing the highest concentration of hyaluronic acid, tempts one to speculate that there may be a connection between these cells and the metabolism of hyaluronic acid.

The supravital staining of these cells with neutral red should be interpreted with care. Although it is generally assumed that this is a characteristic of monocytes and certain

macrophage elements of connective tissues (Tompkins, 1955), other cells, such as plasma and lymphocytes, sometimes show this reaction. Gray (1933) points out that the macrophages evident in vitreous infiltrates do not always give this reaction. Conn (1953) describes the affinity of neutral red and similar dyes for lipids, which would link these staining characteristics to lipid components rather than to phagocytic functions.

Further investigations should clarify the normal function and the pathological significance of the cells in the cortical layer of the adult vitreous body. However, one must bear in mind that the two possible functions, viz., the formation of certain vitreous components, such as hyaluronic acid, and phagocytosis, are not necessarily two separate physiological roles, but functions which may be carried out simultaneously by the same type of cell.

Summary

A short historical survey of the occurrence of cellular components in the vitreous body, with special reference to the cells of the cortical layer in the adult, is given.

These cells have been studied in the eyes of cattle, rabbits, rats, roosters, and humans by phase-contrast microscopy of supravital preparations, by supravital staining, and by observation of the changes induced by the action of fixatives. The cells have also been studied in fixed preparations of the cortical layer, with use of buffered osmic acid and buffered formalin for optimal preservation, and in imbedded samples. Among other staining procedures, the periodic acid-Schiff reaction, lipid staining, and basic dyes were used.

Phase-contrast studies revealed the regular occurrence of these cells on the surface of the vitreous body. In the natural state they are round cells, containing protoplasmic granules and vacuoles, and their nuclei are usually ovoid or kidney-shaped. The granules stain supravitally with neutral red.

Fixed preparations of the vitreous surface showed a regular distribution pattern of these cells, indicating that they may be associated with the retinal vessels. When fixed in buffered osmic acid the cells invariably contained granules, which also were observed under the phase-contrast microscope. These granules showed light blackening with osmic acid, faint staining with Sudan stains, orthochromatic color with basic dyes, and a strong positivity with the periodic acid-Schiff reaction. Hyaluronidase, diastase, and human saliva did not destroy the periodic acid-Schiff positivity of the granules.

The possible functional significance of these cells is discussed, and special attention is given to their macrophage character and to their possible role in the metabolism of the vitreous body.

Miss Gudrun Bergendahl assisted in this investigation. The Boston Eye Bank and its Executive Secretary, Miss June Vine, also cooperated. The Retina Foundation awarded a Retina Foundation Fellowship and the Netherlands Organization for Pure Research contributed for travel expenses to one of us (J. A. S.).

Retina Foundation, 30 Chambers St. (14) (Dr. Balazs).

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A Study of the Relationship Between Adenovirus and Epidemic Keratoconjunctivitis

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Epidemic keratoconjunctivitis (EKC) is an eye disease of well-defined characteristics. The viral nature of this condition had been suspected for a long time from epidemiological studies and from inoculation experiments. Claims of possible isolation of causative viruses have been made by several investigators, but until recently there has been little agreement between the results obtained in different laboratories, and the etiological importance of the reported agents has not been fully established.[1]

In 1955, Jawetz et al.[2] isolated a new adenovirus, Type 8, from a case of EKC. In May, 1956, Mitsui[3] reported the subsequent isolation of a strain of adenovirus Type 8 from a case of EKC in Kumamoto, Japan. Chang[4] isolated a strain of Type 8, as well as several other adenovirus types, from cases of conjunctivitis in children in Saudi Arabia. Subsequently, Mitsui[5] isolated five strains of Type 8 virus from an epidemic during last summer in Kumamoto.

In addition to the isolations of adenovirus Type 8 from typical cases, the close association of this virus with EKC was indicated by the serological studies of Jawetz et al.[6] Ninety-four per cent of persons with a recent history of EKC from America, Europe, and the Orient had neutralizing antibodies against adenovirus Type 8 in their convalescent serum at a dilution of 1:10 or greater. By contrast, about 7% of persons from the same areas having no history of EKC showed such a titer. In most of the adequately paired sera (acute and convalescent) a significant rise in neutralizing antibodies against adenovirus Type 8 was demonstrated during the course of the disease.

Mitsui et al.[7] demonstrated that inoculation of adenovirus Type 8 onto human eyes produced typical clinical EKC, that the same virus was reisolated from the volunteers after the onset of the conjunctivitis, that a significant rise in the neutralizing antibodies against adenovirus Type 8 occurred during the illness produced by this inoculation, and that the person who had neutralizing antibodies against this virus before inoculation did not show any signs of infection after the inoculation.

The purpose of this paper is to report serological and virus-recovery studies on a group of patients with clinical symptoms of EKC.

Materials and Methods

Specimens.—During the period from June to October, 1956, there was a widespread epidemic of EKC in Kumamoto, Japan.[5] It was first mediated through a swimming pool in the downtown area. The Bureau of Health of Kumamoto Prefecture estimated that at least several hundreds of persons were infected during the five-month period. The epidemic picture was complicated by an epidemic of pharyngoconjunctival fever caused by adenovirus Type 3,[8] which occurred in the same city at almost the same season. This epidemic was first mediated through a suburban pool. Both epidemics later spread over the entire city.

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The materials used in this study were collected by Mitsui and his collaborators at the Department of Ophthalmology, Kumamoto University Medical School, and were sent to me at the National Institutes of Health, by air mail, without refrigeration. Specimens were collected from typical and probable EKC patients, and cases of definite pharyngoconjunctival fever were avoided.

Conjunctival material was obtained from four cases of EKC. The conjunctiva was vigorously scraped with a sharp knife edge, with use of topical anesthesia, and the scrapings were suspended in a few drops of modified Mixture 199 * with 10% chicken serum.

Adequately paired sera specimens were also collected from 18 cases of typical and probable EKC, including the 4 cases from which virus material was obtained.

The conjunctival material from two of the four cases was contaminated with fungi during the shipping, and, therefore, these specimens were discarded. The material from two other cases (Patients Segami and Sekiya) arrived in good condition, and viruses were isolated from these.

Clinical Records.—The clinical records of the patients are as follows.[5]

CASE 17.—S. Segami, a 45-year-old woman. An acute follicular conjunctivitis began in her right eye on Aug. 20, 1956. The clinical picture was that of acute follicular conjunctivitis with a tendency to form a pseudomembrane. Monocytes predominated in the discharge. Preauricular adenopathy was not obvious. The conjunctivitis was of about three weeks' duration. There were no systemic symptoms. When examined on Sept. 1, the right cornea demonstrated suspicious subepithelial punctate opacities. They persisted for several weeks, after which time the cornea appeared normal. Epidemiologically, infection with EKC appeared probable.

Conjunctival material was obtained on the third day after onset. Sera were obtained on the 3d and 32d days after onset.

CASE 18.—T. Sekiya, a 14-year-old boy. An acute follicular conjunctivitis started in his left eye on Aug. 19, 1956. Five days later, a similar conjunctivitis appeared in the right eye. The clinical picture was that of a typical acute follicular conjunctivitis with definite preauricular adenopathy. The discharge was fibrinous, and there was a predominance of monocytes. No systemic symptoms occurred throughout the course of the disease. The conjunctivitis lasted about three weeks. By examination on Sept. 4, the development of subepithelial punctate keratitis was suspected on the left cornea. Four days later, the diagnosis of typical subepithelial punctate keratitis was made. The opacities of the cornea persisted for about one month.

The conjunctival material was obtained on the 4th day of conjunctivitis, and sera, on the 4th and 38th days.

Method for Neutralization Tests.—The method used in running virus neutralization tests represents a modification of previous procedures described by Rowe et al.[8] and Jawetz et al.[2] Sera to be tested were first inactivated at 56 C for 30 minutes. Serial twofold dilutions of serum were made up in Mixture 199. The virus suspensions consisted of supernatant fluid from infected KB [10] cell cultures. Viruses were diluted appropriately in HeLa maintenance medium to produce complete cytopathic effect on the third to fifth day. Equal parts of serum dilution and virus dilution were mixed and kept at room temperature for 45 minutes; 0.2 ml. of this mixture was inoculated into each of two monkey kidney cell tubes from which the culture medium had been drained shortly before the procedure. To each of these tubes 0.8 ml. of Mixture 199 was then added. The tubes were incubated at 36 C in a stationary position, and the cells were examined daily for cytopathic effects. Throughout the course of the experiment no change in media was made.

* Mixture 199 is a synthetic tissue culture medium, containing various amino acids and vitamins.[9]

The test results were read as positive or negative 24 hours after the virus control tube (containing virus and medium mixture without antiserum) first showed severe cytopathic changes. The cytopathic effects were graded on a scale of 0 to 4+. Evidence for neutralization was considered definite only when a difference of 2+ in readings was obtained between the control tubes and the serum tubes for more than two consecutive days.

Complement-Fixation Tests.—Complement-fixation tests were performed on paired sera of the EKC patients against adenovirus Types 1 and 8. Complement-fixation tests were performed by Dr. W. P. Rowe and Mr. H. C. Turner, National Institute of Allergy and Infectious Diseases.

Results

Isolation of the Virus in HeLa Cells.—Materials from the two cases described above were inoculated into HeLa-cell cultures. No cytopathic effects were seen during an observation period of eight days. At this time, the tubes were frozen at −50 C, and five weeks later the cells and fluid were passed to fresh HeLa cells. Cytopathic effects developed on the fourth day with the Segami material and on the second day with the Sekiya material.

The identification of the isolated virus was performed under the direction of Dr. W. P. Rowe. The Segami strain was identified as Type 8 and the Sekiya strain as Type 7.[11] Segami virus appeared similar in all regards to Trim virus, the prototype of adenovirus Type 8, first described by Jawetz et al.[2]

In monkey kidney cell cultures the cytopathic effects of Segami and Sekiya viruses seemed to be morphologically distinct. Sekiya virus appeared to produce greater swelling of the cells, which then formed large clumps. The granularity of cells infected with Sekiya virus also appeared to be greater than that observed in cultures of cells infected with the Segami strain.

Serologic Investigations.—The 18 paired sera were tested for neutralizing antibodies against the Segami strain of Type 8, the G. B.† strain of Type 3,[8] and the Sekiya strain of Type 7. Several sera were also tested against the Trim strain of Type 8.[2]

The data thus obtained are summarized in the Table. In 16 of the 18 cases there was a definite rise in neutralizing antibodies against the Segami strain of adenovirus Type 8. In 9 of the 18 cases there was also a rise in neutralizing antibodies against adenovirus Type 3. In six of them (Cases 1, 3, 6, 8, 12, and 15) a simultaneous rise in neutralizing antibodies to adenovirus Type 8 and Type 3 was observed.

Case 2, which did not represent typical EKC clinically, showed no neutralizing antibodies against Segami strain but demonstrated a minimal rise in titer against Type 3 adenovirus. Case 14 had typical EKC with subepithelial punctate keratitis, but very low antibody titers were demonstrated against Segami and Trim strains of Type 8 adenovirus, and no complement-fixing antibody response was observed.

The titer of Type 8 neutralizing antibodies obtained in the convalescent sera of these patients are lower, in general, than those obtained by Jawetz et al.[6] This may be partially due to a difference in the technique; the problem will, therefore, be studied further.

Because of the broad sharing of complement-fixing antigens among adenoviruses, the complement-fixing antibody response of humans is generally not type-specific. However, in the present series, three cases (Cases 4, 5, and 6) did not show complement-fixing antibody response when tested with Type 1 virus but did show a rise of complement-fixing antibody titer with Type 8 virus. Five of the seven EKC patients with opacities tested demonstrated a fourfold rise of antibody against Type 8 virus.

†G. B. strain is the prototype of adenovirus Type 3, described by Rowe et al.[8]; it was supplied by Dr. W. P. Rowe.

Summary of Data

Patient	Age, Yr.	Clinical Symptoms, Opacities	Day of Bleeding	Virus Isolation	Compliment-Fixing Antibody Titer		Neutralizing Antibody Titer			
					Type 1	Type 8	Segami (Type 8)	Trim (Type 8)	G.B. (Type 3)	Sekiya (Type 7)
			3		16	< 8	<10		10	<10
1	12	++	61		64	32	40		20	<10
			3		32		<10		<10	<10
2	9	—	42		>64		<10		10	<10
			9		< 8		<10		<10	<10
3	11	—	38		64		40		>40	<10
			7		< 8	< 8	<10		>10	<10
4	48	++++	31		< 8	16	80		10	<10
			3		< 8	8	<10		>10	<10
5	32	—	35		< 8	16	>40		20	<10
			1		< 8	< 8	< 5	< 5	< 5	<10
6	9	—	36	Type 3*	< 8	64	40	40	40	<10
			5		16		<10		>20	<10
7	12	+	34		32		20		20	<10
			14		< 8	< 8	<10		>10	<10
8	24	±	35		16	16	40		40	<10
			6		32	8	<10		<10	<10
9	24	+++	38		>64	32	10		<20	<10
			3		< 8		<10		<10	<10
10	8	—	49		64		40		20	<10
			2		16		<10		>20	<10
11	54	+	37		32		20		>40	<10
			8		8		<10		10	<10
12	13	—	38		32		20		20	<10
			6		>64		<10	< 5	20	<10
13	23	+	31		>64		20	20	20	<10
			4		< 8	< 8	<10	< 5	20	<10
14	80	++	30		< 8	< 8	10	10	20	<10
			5		< 8	< 8	10		10	<10
15	30	+	29		< 8	< 8	40		20	<10
			3		< 8	< 8	< 5	< 5	80	80
16	58	+++	36	Type 8*	64	64	20	10	80	80
			3		< 8		< 5	< 5	20	>10
17 (Segami)	45	±	32	Type 8	16		20	10	20	20
			4		16	16	<10	10	<10	<10
18 (Sekiya)	14	+	38	Type 7	64	32	<10	20	40	80

* Viruses were isolated by Mitsui.

Comment

In addition to the five strains of adenovirus Type 8 isolated by Mitsui during the Kumamoto epidemic of 1956, another strain of this virus was isolated from the conjunctival scrapings of patient Segami. When paired sera of 18 patients from the same epidemic diagnosed as "EKC with opacities" or "probable EKC without opacities" were tested for neutralizing antibody response to the Segami isolate, 16 (89%) demonstrated a rise in titer. It is significant that 17 of the 18 cases had no Type 8 neutralizing antibody in the serum from the acute phase of the disease. Although the magnitude of antibody titer rise was occasionally low, with a response from <1:5 to 1:10 or 1:20, the occurrence of this low-order rise in one case (Case 16) from whom the virus was actually isolated indicates that the others may also represent homologous responses. With the exception of patient Sekiya, from whom a Type 7 adenovirus was isolated, all 10 of the cases with opacities demonstrated neutralizing antibody response to Type 8. In contrast to the Type 8 responses, 9 of the 18 cases (50%) had some rise in neutralizing antibody to Type 3 adenovirus, and the majority of patients with Type 3 response did not have opacities. Only one case (Sekiya) had a Type 7 response.

The occurrence of heterologous neutralizing antibody responses makes it impossible, in isolated cases, to incriminate a particular adenovirus as the infecting agent on the basis of neutralizing antibody response alone; however, when the majority of cases in the same epidemic show antibody rise to the same adenovirus type it is justifiable to conclude that at least the majority of the cases were indeed infected with that particular type. The association of response to Type 8 alone with the occurrence of keratitis is thus highly indicative that the keratitis patients were actually infected with Type 8. In the cases without opacities, the majority of which had responses to both Type 3 and Type 8, the situation is more complex. No conclusions can be drawn as to whether these represented infections with one or the

other, or both, of these viruses. This is emphasized by the fact that both of these viruses were prevalent in Kumamoto at the time of this study.

Case 6 may well represent a dual or sequential infection with both Type 3 and Type 8. Type 3 was recovered from the eye, but the patient showed neutralizing antibody response to both Type 8 and Type 3, and two other members of the patient's family who had a similar illness had neutralizing antibody responses to Type 8.[5] The rapid growth-rate of Type 3 in tissue culture as compared with Type 8 doubtless would have permitted only the isolation of Type 3 if both were present in the conjunctival specimen.

The data presented in this report supply additional evidence that infection with adenovirus Type 8 may result in the clinical picture of EKC. Although no control cases were included in this series, the isolation of additional strains of adenovirus Type 8 from EKC cases and the almost constant occurrence of neutralizing antibody response to this virus in cases with keratitis provide strong evidence in support of this hypothesis. It cannot be stated, however, that Type 8 adenovirus is the only agent capable of producing the clinical picture of EKC. In fact, patient Sekiya, who was infected with Type 7 adenovirus and gave no indication of Type 8 infection, demonstrated the typical clinical picture of EKC. Whether Type 7 adenovirus was the actual etiologic agent in this case cannot be stated at the present time; however, Ormsby et al.[12] have reported the occurrence of superficial opacities in cases of conjunctivitis due to a variant of Type 7.

Summary

Paired acute- and convalescent-phase serums from 18 patients with typical or atypical epidemic keratoconjunctivitis (EKC) during an epidemic in Kumamoto, Japan, were tested for serological response to viruses of the adenovirus group. In addition, conjunctival specimens from two of the cases with opacities were tested for adenovirus by HeLa-cell inoculation.

Type 8 adenovirus was recovered from one case, and Type 7, from the other. Both of these cases demonstrated antibody responses to the homologous agent.

Ten of eleven cases with corneal opacities demonstrated neutralizing antibody response to Type 8 adenovirus, and they generally did not show a response to Type 3 or Type 7. The one case without antibody response to Type 8 was the case with Type 7 infection.

The seven cases of atypical EKC without opacities generally showed neutralizing antibody response to both Type 8 and Type 3 adenovirus.

It is concluded that the data provide additional evidence of the causative role of Type 8 adenovirus in EKC and suggest that some infections with Type 7 may produce the same clinical picture.

Dr. Wallace P. Rowe, of the National Institute of Allergy and Infectious Diseases, gave guidance and criticism, and Miss J. W. Hartley and Mr. Horace C. Turner, of the same Institute, and Dr. G. R. O'Connor, National Institute of Neurological Diseases and Blindness, gave help and advice. Dr. Yukihiko Mitsui and his collaborators, Kumamoto Medical School, Kumamoto, Japan, made available part of the material used in this study, and coworkers in the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness aided in the study. Mr. Lee Caldwell gave technical assistance.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (14).

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Morphological Study on Alloxan-Induced Cataract

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Previous work on experimental cataract carried out in these laboratories dealt with morphological aspects of the problem and emphasized the sequence of epithelial and fiber pathology as well as the correlation of the histological and cytological changes with biomicroscopic observations in four types of experimental cataract. Experiments on alloxan-diabetic animals were not included in this work in view of the difference in the approach in the alloxan series. Modification comprised low-magnification viewing under the dissecting microscope and observation of the effects of the cataractogenic agent when it had been introduced into the vitreous chamber of the rabbit.

Material and Experimental Procedure

The rat served as experimental animal in the main part of the study. The males of 46 litters of Sprague-Dawley rats (five animals per litter) from the NIH stock were from 23 to 25 days old at the onset of the experiment. The material was divided into five groups consisting of 10 litters each, except for the fifth series, which contained 6 litters. In all experiments four animals per litter received alloxan injections. The remaining rat of the litter was injected with a corresponding volume of 0.9% sodium chloride or—in the last two series—with citrate phosphate buffer. Body weight and food consumption were recorded periodically. The technique of injection was changed in the individual groups because of the high mortality rate in the early experiments and the difficulties encountered in obtaining high blood sugar levels. After a 48-hour fast the animals of the first series were injected intraperitoneally with a dose of alloxan of 35 mg/100 gm. Fasting blood sugar levels were determined by heart puncture according to the method of Nelson and Somogyi [1,2] during the first week after injection. Since the blood sugar level fell within the normal range, a second dose was given on the 10th day and blood sugar levels were measured at the end of the second week. Sixty per cent of the animals died within two days after the second injection. In the second and third series the dose was reduced to 25 mg/100 gm. Sixteen of the forty rats of the second group died. Fasting blood sugar levels were ascertained during the first, second, and third weeks after injection. In the third series two doses of 12.5 mg/100 gm. were injected at an interval of three days. The mortality amounted to 17 of the 40 animals. Since the blood sugar level frequently remained in a normal range, the technique of administration was changed to the method of Klebanoff and Greenbaum,[3] by use of subcutaneous administration of alloxan, 25 mg/100 gm. dissolved in citrate phosphate buffer. Ten of the sixty-four rats of Series 4 and 5 were lost by death. Sixty-nine per cent of the animals had nonfasting blood sugar levels higher than 300 mg. per 100 cc. The blood sugar determinations were carried out during the first week and weekly in most surviving animals.

In all instances biomicroscopic examination on the Goldmann slit lamp preceded the injection procedure; later it was carried out

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at weekly intervals. Experiments were terminated 7, 14, 21, 28, and 35 days after injection. The eyes were prepared for cytological examination on whole mounts of the lens epithelium after use of the Feulgen reaction.[4] The lenses were then examined under the dissecting microscope prior and subsequent to the removal of the lens capsule with the epithelium from the lens body. The changes observed were sketched, in some instances, by the artist. Several times the lenses were bisected meridionally in order to follow closely the distribution of the proliferating nucleated elements in cross section before the histological technique was applied to the celloidin-imbedded material.

The local effects of alloxan, alloxanic acid, and hydrochloric acid solution made up in 0.9% solution of sodium chloride of corresponding pH values were followed in albino rabbits of about 2 kg. weight for about three weeks. The short series comprised four litters of three male animals each and several pilot experiments on past breeders. The chemical compounds were introduced into the vitreous in quantities of 0.2 ml. following paracentesis. Details of the technique will be presented with the results of this group of experiments.

Results

Biomicroscopic Observations.—Two types of initial changes occurred in 230 lenses which were observed in animals one week or longer after the alloxan injection. In the majority of preparations the earliest lesion formed a complete or partial ring close to the equator which consisted of densely arranged short radial striae of a silky luster. In some instances small vacuoles were dispersed in this zone, but as a rule typical subcapsular vacuoles developed a few days later and increased in size and number, with a concomitant disappearence of the striate opacities. In this later stage the ring of vacuoles resembled that seen in galactose cataract. In the following weeks the vacuoles tended to confluate, to decrease in number, and finally to disappear, leaving a diffuse fine opacity behind them. A second initial or early lesion began to develop near the surface portion of the anterior suture system. It evolved from indistinct grayish patches or a diffuse haze and assumed a star, Y-, or circular shape around the anterior pole. Occasionally a faint halo was detected underneath this opacity. The characteristic changes later gave way to spoke- or sector-shaped opacities of the anterior lens cortex, as in other advanced stages of experimental cataract. As long as a relative transparency of the anterior cortical layers permitted inspection, the lens nucleus and the posterior cortex remained clear. The described subtle opacification around the anterior pole preceded in 18 instances the appearance of the peripheral changes or the latter were not visualized at all during the five weeks after injection of the compound.

Observations on Feulgen-Stained Lenses Under Dissecting Microscope.—The lenses were removed from the eyes, which had been fixed in Carnoy's solution, and processed according to the usual Feulgen technique designed for such material. When examined under the × 45 magnification of the dissecting microscope in the focused beam of a Zeiss operation lamp, fiber swelling and superficial vacuoles in the lens cortex were invisible, but valuable information on the distribution of cells or cell nuclei was gained by examining, first, the anterior and posterior aspect of the whole lens; second, the lens after removal of the capsule with the adherent epithelium, and, third, in several instances, the meridionally bisected lens body. Lenses of 51 rats were observed with this technique. The star- or Y-shaped polygonal or circular opacities, described in the preceding paragraph, were shown to consist of heaped-up nucleated cells or cell nuclei. This accumulation of cells or cell components could be separated into two parts. A superficial portion apparently originated from a dense grouping of surface epithelial cells along and around the anterior suture system. It will be shown later that the

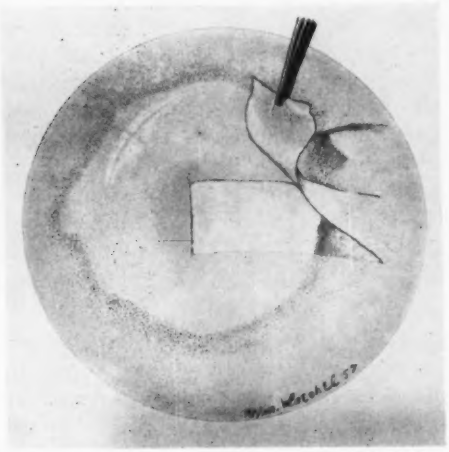


Fig. 1.—Drawing of anterior aspect of lens removed five weeks after alloxan injection. Observed through dissecting microscope. Nonfasting blood sugar level 483 mg. per 100 cc. Central area suggests dense grouping of epithelial cells. A deep layer of cell nuclei is especially well seen when the lens capsule and the epithelium is incised and lifted back. It consists of cell nuclei which have migrated forward from the bow area. Feulgen stain.

histological examination modified this impression. By deeper focusing a second layer of cell nuclei was discerned (Fig. 1). It proved to be formed by forward extensions of the bow nuclei when the capsule and epithelium had been removed to be used for whole mounts. These nuclei covered either a homogeneous ring zone, which tended to progress with time in the direction towards the anterior pole, or appeared in form of radial strands.

In the advanced state the most forward or marginal part of this layer of nuclei assumed a darker purplish color as these cell constituents seemed to line the walls of the suture system and to merge with the proliferated surface cells. The initial phase of the forward migration of bow nuclei and the onset of proliferation of surface cells were noted already at the one-week interval in several preparations.

In contrast to the conspicuous unidirectional displacement of bow nuclei in the superficial layers of the anterior cortex and the proliferation of surface cells around the anterior pole or at other focal areas of the epithelium, the posterior aspect of the lens was free of nucleated elements The posterior margin of the bow was sharply de-

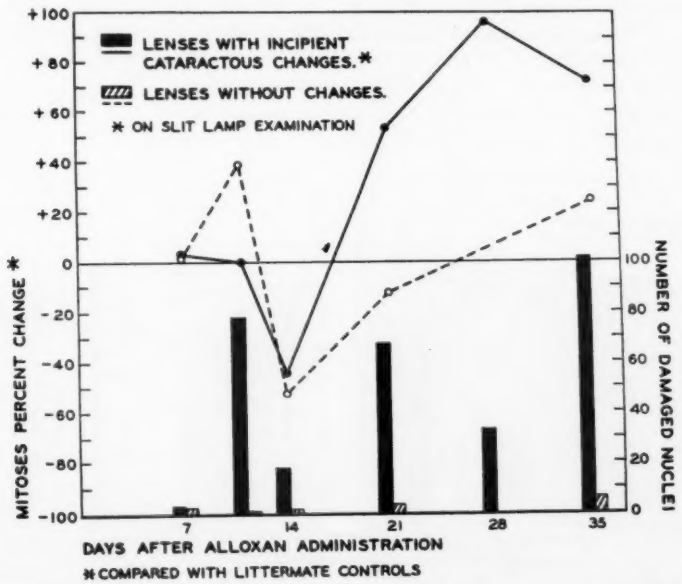


Fig. 2.—Effect of alloxan administration on mitotic rate and extrusion of Feulgen-positive material in the lens epithelium of rats.

marcated and only occasionally exhibited garland-shaped irregularities. Examinations with the higher power of the light microscope confirmed the analysis of these semigross observations.

Observations on Whole Mounts of the Lens Epithelium.—The effect of systemic alloxan administration on mitotic activity and on cell degeneration of the lens is illustrated in Figure 2. More than 100 preparations were used for averaging the individual data in the subgroups. The graph shows separately the results for animals with cataractous lesions and for animals free of such changes, independent of the measured blood sugar levels. When the figures were compared with those obtained on normal litter mates, it seemed that the second group responded to alloxan with a moderate increase followed by a fall of the average number of dividing cells, but the listed numbers represent only the counts of two preparations each; as a rule, from 4 to 32 preparations were available for averaging the pertinent data on the behavior of the epithelium in the various groups. The animals with biomicroscopically visible lesions, even of minimal degree, lacked the phenomenon of overshooting mitosis at the one-week period. However, in the present study no counts were made within the first week after alloxan administration. The depression of cell division in the two groups during the second and third week was similar, but the subsequent overcompensating increase of mitosis in the animals with incipient cataractous changes exceeded by a multiple that in the other group; at the four-week interval dividing cells about doubled the number counted in control litter mates. In clear lenses the mitotic rate was normal at this time and rose to a 25% increase by the end of the fifth week after alloxan injection. Figure 3 provides evidence for the changes of mitotic activity of animals with blood sugar levels above 350 mg. per 100 cc. As compared with the results shown in Figure 1, the main difference rests in the absence of a depression of mitosis in the second and third week. The curve rose steadily from the second-week interval and was still 70% above the range determined in the control animals at the five-week period.

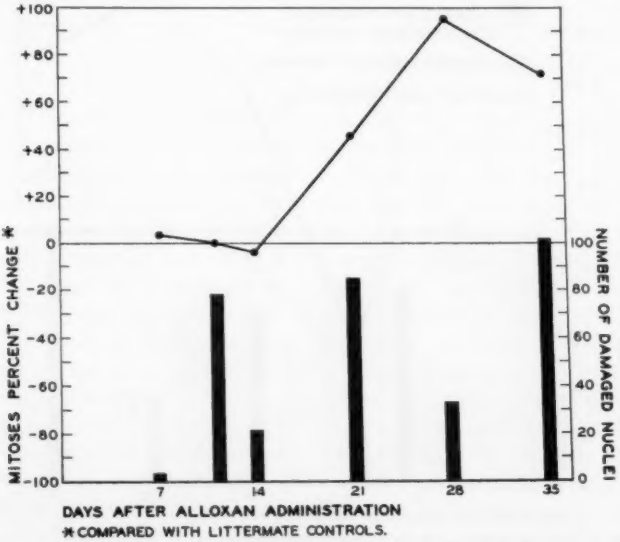


Fig. 3.—Effect of alloxan administration on mitotic rate and extrusion of Feulgen-positive material in the lens epithelium of rats with incipient cataractous changes and blood sugar levels over 300 mg. per 100 cc.

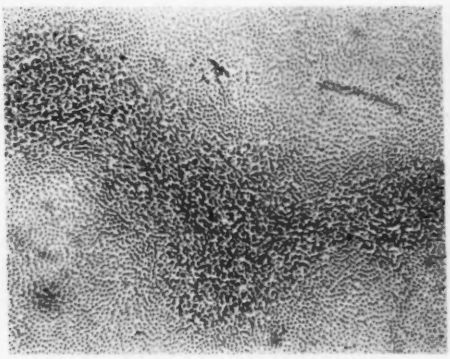


Fig. 4.—Dense arrangement and duplication of epithelial cells in area of anterior pole of lens. It is the substrate of Y- or polygonal-shaped early lens opacities. Five weeks after alloxan injection. Non-fasting blood sugar level 483 mg. per 100 cc. Whole mount, Feulgen stain; reduced about 1/6 from mag. × 100.

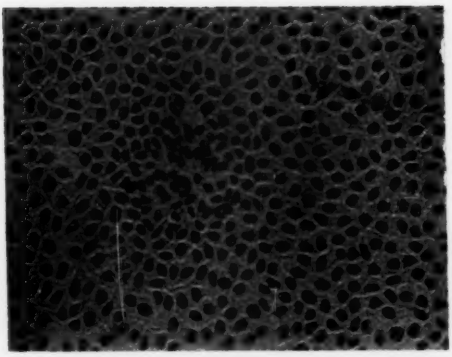


Fig. 5.—Incipient focal accumulation of epithelial cells in preequatorial zone. Seven days after alloxan injection. Nonfasting blood sugar level 423 mg. per 100 cc. Whole mount, Feulgen stain; reduced about 1/6 from mag. × 160.

The main discrepancy between the results of clear and cataractous lenses related to extent of cell degeneration (Fig. 2). In clear lenses abnormal cells scarcely surpassed those encountered in control litter mates. Preparations from lenses with biomicroscopically visible fine opacities contained many degenerate cells. Their number rose steeply after the 7th day and reached a peak on the 35th day, at the end of the experiment. The steady increase of the change was interrupted by relatively low counts at the 14- and 28-day intervals.

Whereas nuclear fragmentation in other types of experimental cataract predominates in the preequatorial and equatorial zone of the epithelium, in the present series it excelled at the "foci" of the central area where cell proliferation and duplication took place. These flat mounts of the lens epithelium lend themselves well to show the amassing of surface epithelial cells around the anterior lens pole and other scattered sites and the correlation with the patterns of opacities observed with the corneal microscope. This is illustrated in Figures 4 to 7.

Histological Observations.—The microscopic observation of sections of 32 lenses served for comparing the alloxan-induced

Fig. 6.—Advanced focal accumulation of epithelial cells with extrusion of chromatin material in preequatorial area. Twelve days after alloxan injection. Fasting blood sugar level 322 mg. per 100 cc. Whole mount, Feulgen stain; reduced about 1/6 from mag. × 160.

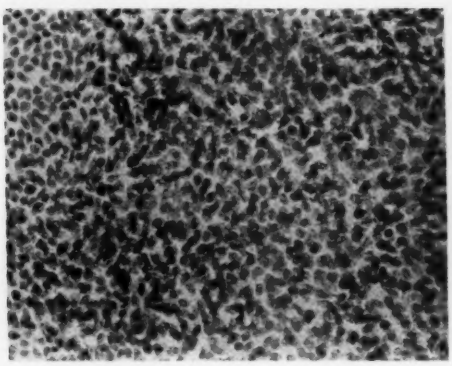
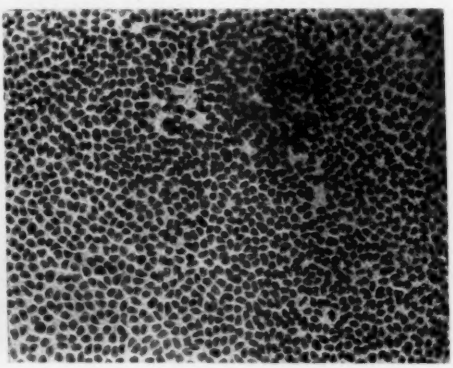


Fig. 7.—Advanced focal accumulation of epithelial cells in equatorial area. One week after alloxan injection. Nonfasting blood sugar level 423 mg. per 100 cc. Whole mount, Feulgen stain; reduced about 1/6 from mag. × 160.



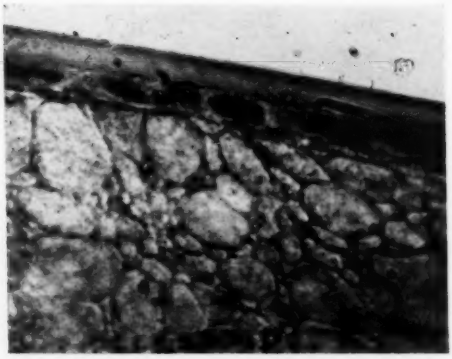


Fig. 8.—Cross section of hydropic fibers under anterior lens capsule. Seven days after alloxan injection. Nonfasting blood sugar level 794 mg. per 100 cc. Hematoxylin and eosin stain; reduced about 1/6 from mag. × 2000.

histopatholgy of the lens with biomicroscopic findings and with those obtained with the dissecting microscope on the Feulgen-stained preparations. Moreover, the relation of these changes to variations of mitotic activity and the extent of nuclear fragmentation was made possible by processing the second, similarly involved, eye of 21 animals according to the technique employed for whole mounts of the epithelium.

The earliest fiber change at the seven-day interval related to the abnormal appearance of the subcapsular endings of the fibers at the anterior suture system (Fig. 8) and of the equatorial portions of fibers in deeper layers of the lens cortex (Figs. 9, 10A, and 10B). In several preparations granular debris replaced the regular fiber architecture at the equatorial site (Fig. 9). This disintegration of the cytoplasm led to vacuolation and, by confluence of small vacuoles, to the development of large cystic spaces. In some sections the cavities contained granular matter (Fig. 10A). At the early period and in the following weeks the cystic spaces were confined to a layer midway between capsule and the nucleus of the lens, with morphologically normal fibers and bow nuclei in juxtaposition, both centrally and peripherally (Fig. 10B). Foremost in the fiber histopathology during the following period was the excessive swelling of these cell components in the anterior cortex, matched, in the most advanced stages only, by analogous changes in the posterior cortex.

The sections showed multilayered arrays of the epithelium, mostly at and around the anterior pole (Fig. 11), but occasionally also in a patchy or diffuse pattern at other sites on the anterior surface of the lens. In the studied stages of alloxan-induced damage the changes were always restricted to the anterior half of the lens. Displacement of bow nuclei was strictly directed forward and progressed from the second and third week after administration of the drug toward the anterior pole (Fig. 12). The advanced nuclei usually spread out in a layer located at a short distance from the surface epithelium. In four lenses the direction of the forward displacement of the bow nuclei reversed itself at a point close to the anterior pole, with a swing of these

Fig. 9.—Incipient fiber damage in middle layers of bow area consisting of granular light droplets. Note normal adjacent fibers. Seven days after alloxan injection. Fasting blood sugar level 147 mg. per 100 cc. Hematoxylin and eosin stain; reduced slightly from mag. × 950.

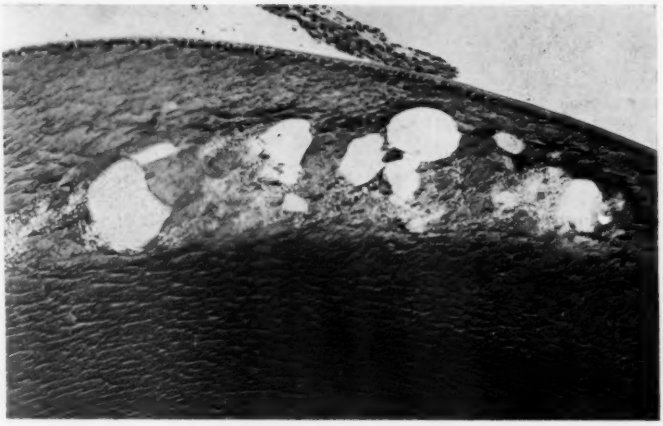


Fig. 10A.—Early stage of fiber destruction in middle layers of bow area. The small droplets confluate to larger vacuoles. Some of them are filled with granular debris. One week after alloxan injection. Nonfasting blood sugar level 794 mg. per 100 cc. Hematoxylin and eosin stain; reduced about 1/3 from mag. × 500.

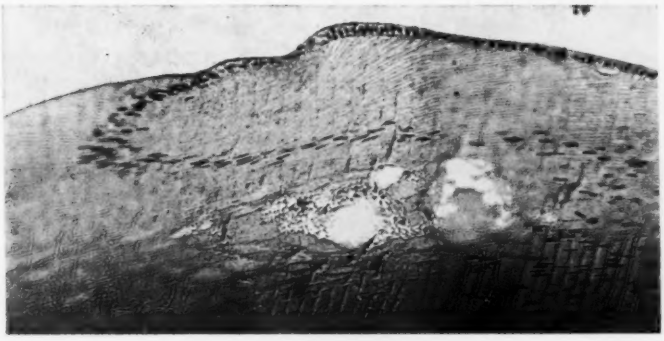


Fig. 10B.—Eleven days after alloxan injection. Nonfasting blood sugar level 385 mg. per 100 cc. Note the normal architecture of adjacent layers. Hematoxylin and eosin stain; reduced about 1/3 from mag. × 200.

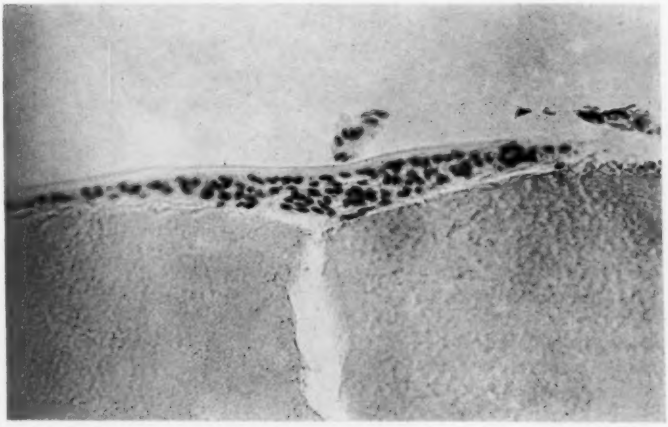


Fig. 11.—Multilayered epithelial proliferation at anterior pole of lens in front of gaping suture. Four weeks after alloxan injection. Nonfasting blood sugar level 418 mg. per 100 cc. Hematoxylin and eosin stain; reduced about ½ from mag. × 400.

tissue elements backward to form in cross section the shape of a flattened and slightly distorted S (Fig. 13). Frequently the most anteriorly migrated nuclei blended with the proliferated surface epithelial cells at the anterior pole. Another variant of the bow architecture consisted of a subdivision of the simple curve of the bow into two cres-

Fig. 12.—Multilayered epithelial proliferation at and around anterior lens pole blending with forward-migrated bow nuclei. Extensive fiber hydrops in neighboring areas. Five weeks after alloxan injection. Nonfasting blood sugar level 576 mg. per 100 cc. Hematoxylin and eosin stain; reduced about ½ from mag. × 240.

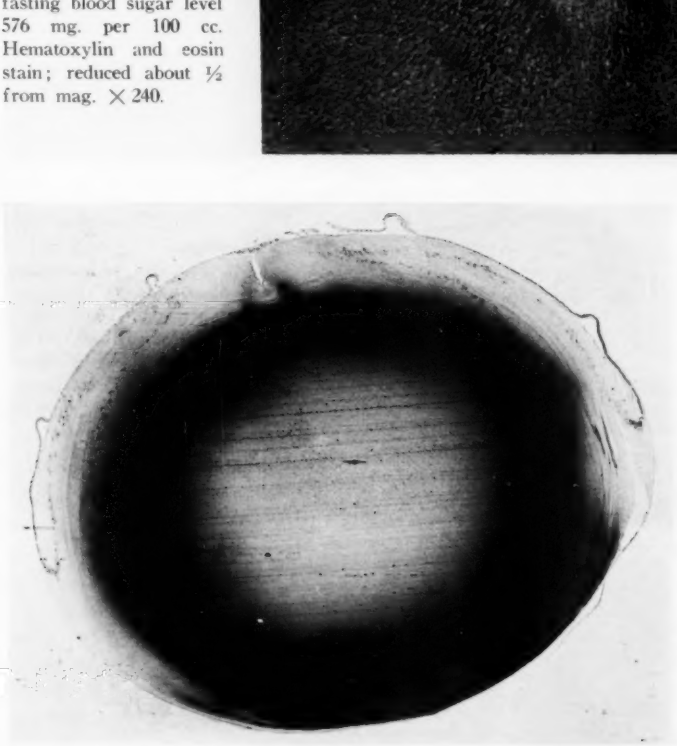


Fig. 13.—S-shaped arrangement of bow nuclei. The forward-migrated nuclei almost reach anterior pole of lens. Four weeks after alloxan injection. Nonfasting blood sugar level 418 mg. per 100 cc. Hematoxylin and eosin stain; reduced slightly from mag. × 40.

Fig. 14.—Bow area with abnormally backward displaced nuclei in deeper part with hydropic swelling of fibers in this layer. Four weeks after alloxan injection. Nonfasting blood sugar level 540 mg. per 100 cc. Hematoxylin and eosin stain; reduced slightly from mag. × 200.

cent-shaped parts, as illustrated in Figure 14.

Histological examination of lenses removed 7 to 10 days after the alloxan injection indicated, then, that the early diffuse or patchy haze, seen with the slit lamp, was brought about by the hydropic swelling of the anterior ends of the superficial lens fibers. The examination further suggested that hydropic swelling or granular decomposition of the fibers in deeper cortical layers in front of the lens bow is the substrate of the fine radial silky striation at the equator, as described in the paragraph on biomicroscopic changes.

The vacuoles, seen clinically, derived from the progressive destruction of part of the fibers in a relatively circumscribed area in deeper layers of the cortex in front of or partly interrupting the arch of the bow cells. Fibers and nuclei between this zone and the capsule exhibited normal morphology and spatial distribution.

The microscopic examination confirmed the impression obtained at low magnification under the dissecting microscope; it showed that the surface epithelial cells piled up in several layers around and along the anterior suture system and, thus, produced the star-shaped or circular opacities at an early date; the forward displacement of bow cells caused the subtle diffuse opacity underneath.

The described histopathology existed, with a few exceptions, in rats in which alloxan administration had produced hyperglycemia amounting to more than 350 mg. per 100 cc. In the two instances with low blood sugar levels the possibility cannot be excluded that the sugar determination was at fault.

Preliminary Experiments on Rabbits with Intravitreal Injection of Alloxan and Alloxanic Acid.—In this group of experiments the intravitreally injected rabbits were examined weekly with the slit lamp and killed from 12 to 25 days after the administration of the following solutions: isotonic alloxan (0.2 to 0.4 ml.), five eyes; isotonic alloxanic acid (0.2 ml.), four eyes; 0.9% solution of sodium chloride at pH 7 (0.2 ml.), one eye; isotonic solution of hydrochloric acid at pH 1.2 (0.2 ml.), two eyes. Histologic examination was carried out on two globes. In the remaining lenses an equatorial incision of the Feulgen-stained preparation severed the anterior from the posterior half of the lens capsule with adherent epithelium. The two portions were mounted separately for counting of dividing and degenerate cells.

In three pilot experiments on past breeders alloxan injection gave rise to the formation of moderate veil or cellular vitreous opacities. No lens changes were noticed in these animals. Low-power microscopy on the lens of one eye which had received two

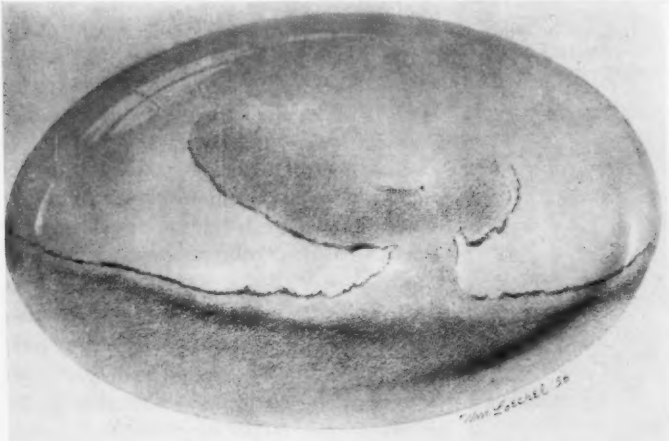
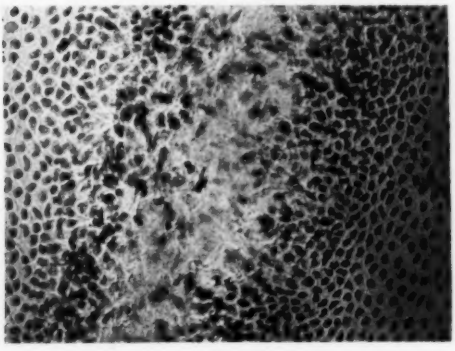


Fig. 15.—Drawing of epithelial cells proliferating towards the posterior lens pole. Three weeks after injection of alloxan in rabbit vitreous. Observed through dissecting microscope. Feulgen stain.

injections of alloxan revealed, after completion of the Feulgen reaction, proliferation of surface epithelium, which lined a complete broad sector of the posterior capsule (Fig. 15). The number of dividing cells (208) and degenerate cells (164) under the posterior capsule contrasted with a low count (dividing cells, 25; degenerate cells, 4) under the anterior capsule. In four preparations from eyes injected with 0.2 ml. of alloxan the number of dividing cells (6 to 12) and degenerate cells (1 to 3) was low in the posterior portion of the preparation three weeks after injection. A fine striate opacity perpendicular to the posterior horizontal suture characterized the biomicroscopic picture in these eyes. Histologically it consisted of hydropic portions of subcapsular fibers around the posterior lens pole.

Injection of isotonic alloxanic acid and isotonic solution of hydrochloric acid of pH 1.2 gave rise to a violent inflammatory reaction, predominantly in the posterior segment of the eye. A dense opacity developed in the posterior cortex during the first week, and in the following two weeks the anterior cortex became also partially cataractous. The histologic picture was dominated by extensive fiber damage in the posterior cortex. Its surface was lined with an almost continuous layer of relatively well-preserved epithelial cells, with many mitoses and degenerate cells. The number of dividing cells ranged from 114 to 320 in the posterior half but was depressed in the anterior portion. There were 169 to 413 cells with nuclear fragmentation counted posteriorly, and 29 to 275 were counted anteriorly. The equator showed severe destruction and was occupied by a broad amorphous Feulgen-positive zone (Fig. 16). The results of these experiments are not tabulated because of their preliminary nature.

Fig. 16.—Distruction of equatorial zone. Three weeks after injection of alloxanic acid in vitreous of rabbit. Note proliferation of regular layer of epithelium underneath posterior capsule at left. Whole mount, Feulgen reaction; reduced about 1/6 from mag. × 160.



Comment

This study is a part of an investigation which had as its aim the determination of the role the epithelium plays in the pathogenesis of experimental and senile cataract.[5] The literature on lens changes in alloxan diabetes—first described in rabbits by Bailey, Bailey, and Leech[6]—is extensive. Attention has been paid to clinical and histological morphology in the past in many contributions.[7-10] Yet a clear appreciation of changes in the epithelial layers and the bow nuclei in the cataractous process is lacking. It stimulated the present investigation, with the purpose of studying and relating epithelial and bow pathology with the fiber changes and identifying the anatomical substrate of the clinically observed opacities. Specifically, it was hoped to narrow the gap in the knowledge of the pathogenesis of alloxan cataract by the combined use of several technical procedures, such as biomicroscopy, cytological examination of flat mounts of the epithelium, observation of whole Feulgen-stained lenses at low magnification, and microscopic examination under high power. Furthermore, controlled conditions of work on litter mates in sufficiently large series provided the basis for arriving at safe conclusions.

In the main part of the study alloxan was administered systemically in rats and was used tentatively in the form of intravitreal injections in rabbits in a small group of experiments. The deductions made from the results of the rat experiments corroborate

in several respects the findings of early investigations as far as the parameters of the studies coincide. In other instances they deviated from previous reports. It is surprising, however, that the points of agreement outweigh those of discordance when the differences of strain, species, and age of the experimental animals; of the technique of alloxan administration; of the procedure to establish the diagnosis of early lens opacities, and of the state of cataract used as criterion for lens damage are taken into account. Since in this paper the systemic use of alloxan was limited to the rat, no reference will be made to lens damage described in rabbits, mice, or dogs, despite the apparent similarities of the slit-lamp and histological changes in these species. Pertinent biomicroscopic observations on the rat have been given by Bellows and Shoch [7]; Kok-Van Alphen and Cohen [11]; Janes, Bounds, and Leinfelder [12]; Babel,[8] and Bounds, Janes, and Leinfelder.[10]

Analysis of fiber and cell changes and their relation to the biomicroscopic picture could be conducted more successfully in the alloxan rats than in previous work because of the addition of one or two new methods of examination. Among the types of lenticular opacities studied, alloxan cataract, as stated previously by other workers,[8,10] most closely resembles the galactose-induced lens damage, as far as early hydropic swelling of fibers and vacuolation at certain areas are concerned. Lenticular changes in the alloxan-treated rat, however, are at variance with reported observations on any other type of studied experimental cataract with respect to the patchy or focal arrangement of proliferating and degenerate cells in the epithelium and the extent of the unidirectional migration of the bow nuclei. It is of interest and reminiscent of galactose cataract that the germinative area does not lose its capacity to form new healthy lens fibers, despite the severe damage at a neighboring zone in the bow area. The reported therapeutic effect of insulin treatment for the restoration of lens transparency in early stages of the cataractous process [13-15] is reflected in the morphologic integrity of this part of the germinative zone.

The description of the slit-lamp view of the early lens lesion by Bellows and Shoch [7] is almost identical to that presented here. However, these workers explained the Y-shaped or triangular opacities by the uptake of water at the suture lines and its diffusion into the adjacent fibers. It was shown in the current study that the lens epithelium is strongly implicated in the cause of these opacities. Bellows and Shoch [7] and Bounds, Janes, and Leinfelder [10] illustrated the histologic picture of duplication of the epithelium at the anterior pole, an observation which was fully confirmed in the present investigation. This multilayered piling up of the epithelium, however, occasionally involves, in a diffuse or patchy fashion, other areas of this cell layer. Early hydropic swelling of lens fibers at the equator and near the anterior surface has been emphasized by Friedenwald and Rytel,[9] and the vulnerability of the subcapsular young fibers at the lens equator has been remarked on by Babel.[8] This statement needs modification, as the youngest, most superficial, fibers appear not to be damaged by the toxic agent; the area of hydropic swelling and disintegration of the fibers is regularly noted in the deeper part of the cortex at the bow area and is separated from the surface by a layer of normal fibers and nuclei. No explanation can be given at present for this selective topography of early injury to elements in a rather protected area of the lens.

The activity of the bow nuclei and their advancement towards the anterior pole has not been previously related to the cataractous process. It could be argued that the migration of these cell components and the surface epithelium proliferation which follows the development of fiber hydrops promptly, or coexists with this lesion, indicates a protective function of these tissue elements. The acceptance of such a relationship would tend to underestimate the

perplexities of the situation. Heaping up of epithelial cells in focal areas was not clearly connected with the pathology of underlying fibers, and, vice versa, sites of localized fiber damage were often covered by normal epithelium. The possibility must be entertained, then, that the two forms of tissue injury are coordinate rather than causatively correlated. In contrast to the information contained in the literature,[8,10,12] fibers in the posterior cortex preserved their morphological integrity except in advanced stages of cataract formation; no cell proliferation in this part of the lens occurred in the five-week period.

Cell degeneration and cell division was excessive in the area of the anterior pole, similar to the observation on other types of experimental cataract, in which extreme mitotic activity coincided with the increase of cell degeneration. The number of cells with extrusion of Feulgen-positive material was of the same magnitude as that counted in galactose cataract and less pronounced than in radiation damage produced by 1000 r x-ray and in busulfan (Myleran) cataract.[5]

Injection of alloxan and alloxanic acid in the vitreous in order to study the effect of these components on the lens might appear unrelated to the problem of the cataract formation in alloxan-diabetic animals. However, the pattern of epithelial damage does not exclude a particular susceptibility of the cells to whatever the offending noxious agent may be. It has been concluded by Patterson,[16-22] from the results of his extensive investigative work in this field, that hyperglycemia cannot be considered the direct mediator for the development of cataract, although it regularly accompanies the evolution of the lens pathology and is thought to be the causative factor by the great majority of investigators. In discussing the topical use of alloxan it is appropriate to refer to the fact that the mechanism by which alloxan produces selectively—within minutes—the injury of the beta cells in the island tissues of the pancreas is unexplained and that this injury leads to disintegration of these cells by six hours, at the onset of the hypoglycemic phase.

The results of the experiments with intravitreal administration of alloxan, alloxanic acid, and isotonic solutions of hydrochloric acid at corresponding pH values are too incomplete to be reviewed, but the subcapsular proliferation of the epithelium elicited by these compounds and confined to the posterior half of the lens deserves mention. The question whether pH changes or specific chemical action produces this effect is unanswerable at present. It has been mentioned by Bounds, Janes, and Leinfelder[10] and confirmed in this study that apparently clear lens may exhibit morphologic changes upon examination. It remains to be seen whether Mandel and his co-workers' observations[23-25] on clear rabbit and rat lenses of an increase in adenosine triphosphatase activity, augmented ability to consume pyruvic acid, and the depression of hexokinase activity eight days after alloxan injection apply to the normal histology of this material. From the technique used and the time interval which had elapsed after injection, it would be expected that fibers and epithelium had undergone changes at the time of chemical analysis.

Summary

The morphology of incipient alloxan-induced cataract has been studied systematically under controlled conditions by comparing the results of various technical approaches to the problem.

Biomicroscopically visible signs of early lens damage could be analyzed histologically as to the participation of epithelium, fibers, and bow nuclei in the pathologic process.

The histopathologic changes in early stages are limited to the anterior cortical layers and consist, at the very onset, of hydropic swelling of lens fibers with subsequent disintegration of the cytoplasm and proliferation of the epithelium.

The areas of predilection for the fiber damage are located in deeply seated portions

of fibers at or in front of the lens bow and at anterior subcapsular endings of fibers predominantly around the suture system.

The peripheral stratum of the germinative area did not seem to lose its capacity to provide new fibers at a time when extensive cataractous changes had taken place in the anterior and posterior cortex.

The patchy areas of epithelial cells at the anterior pole and occasionally at other sites of the cell layer are not clearly related to fiber pathology and distinguish alloxan-induced cataract from other experimentally induced lenticular opacities.

Since the chemical mechanism which results in the lens damage of alloxan-diabetic animals is not known and since it is unlikely that hyperglycemia by itself mediates the production of cataract, experiments on the local effects of alloxan and alloxanic acid were initiated, but the problem requires further investigation.

Mr. Fred Meiller did the microphotographic work in this study.

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Treatment of Experimental Herpes Simplex Iridocyclitis with Human Serum Gamma-Globulin

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Herpetic infection of the eye constitutes one of the commoner and less responsive therapeutic problems faced by the ophthalmologist. The incidence and clinical features of this disease were catalogued by Gundersen [1] in his classic paper published more than 20 years ago. Thygeson, Kimura, and Hogan [2] have reviewed recent developments and have set forth the current status of the problem of herpes oculi. From these studies, it appears that herpes corneae may actually be increasing in frequency, that its complications are increasing in severity (partly as a result of injudicious treatment with corticosteroids), and that no specific chemotherapy exists for this disease.

The ecology of herpes simplex virus in human beings has been elucidated by Burnet [3] and has been reviewed by Blank and Rake.[4] Antibody surveys of various populations have shown a neutralization of herpes simplex by the sera of high percentages of persons. Uniformity of antiherpes activity in human γ-globulin samples from different geographic regions was demonstrated by Heyl, Allen, and Cheever.[5] In the "in vivo" counterpart of these studies, Cheever and Daikos [6] demonstrated only a minimal prophylactic effect of human γ-globulin against experimental herpes encephalitis in mice.

During the past 10 years, ophthalmologists have used human γ-globulin both topically and parenterally against herpes corneae in humans. The results have been disappointing in the majority of cases. We attribute failure of this treatment to (1) inaccessibility of intracellular virus to extracellular antibody and (2) avascularity of the normal cornea. There were, however, a few cases in which parenteral γ-globulin therapy was followed by a rapid marked subjective and objective improvement far greater than could have been expected to occur spontaneously from the course of the disease up to that point. The common feature of all these cases was that the cornea was vascularized as a result of prior or long-standing herpetic infection.

These observations suggested an evaluation of the therapeutic significance of parenteral γ-globulin in ocular herpes; the anterior uveal tract was selected as the site for study because of its vascularity. Injection of herpes simplex virus into the anterior chamber of a rabbit's eye results in a specific inflammation of the iris, characterized by edema, hyperemia, and ciliary congestion. Stromal edema of the cornea is a fairly constant accompaniment of the iritis; no primary nor secondary dendritic involvement of the corneal epithelium has been observed in any animal. In some rabbits the disease progresses to encephalitis and death. In the surviving animals spontaneous resolution of the process occurs, with a minimum of residual signs. The course of the disease is sufficiently distinctive to permit reliable clinical observations to be made.

Materials

Virus Agent.—The stock Zaccardi strain X569A of herpes simplex virus * was used throughout the experiment. The virus was

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* Dr. John F. Enders provided this virus.

present in a 10^{-1} suspension of chick embryo in CAF (5% beef embryo extract, 5% horse serum, and 90% cow amniotic fluid, containing 50 units of penicillin per milliliter and 0.005 ml. of soybean trypsin inhibitor per milliliter) and had an infective titer of 10^{-3} to 10^{-4} for chick embryo tissue. The suspension was tubed in 1 ml. aliquots and stored at −70 C. A single 1 ml. portion was used to inoculate all eyes in a given series.

Globulin Preparation.—Human serum γ-globulin (Cutter Laboratories, Berkeley, Calif., Lot 646-12) from venous nonplacental blood was used. The preparation contained 165 mg. of γ-globulin per cubic centimeter and was preserved with thimerosal 1:10,000.

Rabbits.—Normal 3 to 4 kg. New Zealand albino rabbits of both sexes representing a single strain were obtained from the Benson Farm, Hopkinton, Mass.

Methods

Technique of Virus Inoculation.—With the animal anesthetized with pentobarbital sodium the anterior chamber was entered with a 27-gauge needle through a slanting track in the corneal periphery and 0.04 cc. of aqueous was withdrawn. Then 0.03 cc. of virus or heated control suspension was inoculated into the chamber through the same track. With practice, this procedure was accomplished with a minimum of trauma to the eye. The experiment was run in five series of eight rabbits each. The first three series received the virus suspension in one eye and the heated suspension in the other (see controls), while the remaining two series were inoculated in both eyes with virus suspension.

Technique of Globulin Injection.—Five cubic centimeters of undiluted globulin was injected intraperitoneally into each treated animal. In the first four series this globulin injection preceded inoculation of the virus by 24 hours. In the fifth series the globulin was given on the third day after inoculation. The intraperitoneal injection of globulin was well tolerated by all animals.

Observations.—The animals were observed daily, and the gross appearance of the eyes was recorded. The eyes were examined with the biomicroscope at first, but this was discontinued when it appeared that macroscopic evalution was sufficient. The severity of the reaction was rated from 0 to 4+. Objective criteria for the ratings were iris hyperemia, ciliary congestion, corneal edema, and conjunctival exudate. Checks were made at irregular intervals by an observer unaware of the identity of the individual animals.

Controls.—The specificity of the infection was established by the absence of pathogenic bacteria in cultures of the virus suspension and by the injection of a control suspension of virus heated to 60 C for one hour in the fellow eye of animals in the first three series. Variation in the potency of individual doses was excluded by the use of a single aliquot of virus to infect all animals in a given series.

The rabbits to be treated were selected at random, i. e., the rabbits were numbered and cards with corresponding numbers were mixed and drawn.

Rabbits were isolated in individual cages; this fact, as well as the intraocular nature of the infection, eliminated the possibility of cross infection. In none of the first three series was there any reaction in the control eye which could have been attributed to infection from the fellow eye. Each experimental series included parallel control animals, and so environmental factors were identical in the case of treated and untreated animals.

Results

Control Eyes.—Slight iris hyperemia and mild ciliary congestion were present on the day following the inoculation of the heated virus suspension. The reaction subsided rapidly, and these eyes presented a normal appearance by the second day.

TABLE 1.—*Sample Protocol on Day 8 (Series 2)*

Nontreated rabbits	Rating
1	++++
2	++++
3	++
4	++
Treated rabbits	
5	+
6	++++
7	++
8	+

Infected Eyes.—Instead of subsiding after the trauma of inoculation, the reaction progressed to a stage of moderate to marked edema and hyperemia of the iris, engorgement of the circumcorneal vascular ring, and stromal edema of the cornea. This stage reached its height in two to three days in all eyes and then continued at the same level. Few untreated eyes showed recovery before the eighth or ninth day. The signs gradually diminished and disappeared by the 14th day. Irregularity of the pupil from posterior synechiae was the only residual lesion and occurred in 60% to 75% of cases.

In most animals receiving γ-globulin there was a quantitative improvement from the fifth day onward. This occurred at the same time in animals which received the globulin before inoculation as it did in those receiving globulin after infection had developed.

Analysis.—The ratings were recorded on a protocol as illustrated in Table 1. For purposes of statistical evaluation of the series, an eye rated 0 to 1+ was considered to have recovered, while one rated 2+ to 4+ was not.

The cumulative data from the treated animals were compared with the data from the untreated ones. It appeared that the eyes of treated animals showed an actual difference in the course of the disease. Since almost all the eyes had recovered by two weeks, comparison of end-results offered no information. Therefore, the daily results were subjected to a χ^2-analysis to determine whether the course of the disease had been modified. The method of analysis as applied to the data from Table 1 is shown in Table 2.

TABLE 2.—*Chi-Square Determination for Data of Table 1*

	Recovered (0-1+)	Inflamed (2+-4+)
γ-Globulin treated	2	2
Nontreated	0	4
	$\chi^2 = 2.67$	

The cumulative results of the four series in which γ-globulin was given before inoculation were analyzed, and the χ^2 values are recorded in the second column of Table 3. P (probability that chance could account for the result) values are recorded in the third column. The χ^2 and P values for the fifth series (treated after inoculation) are recorded in Columns 4 and 5, respectively.

In the pretreated animals (Table 3, Column 3) chance could have been responsible for the improvement less than 5 times in 100 from the fifth day to the eighth. The animals treated after inoculation (Table 3, Column 5) show significant values of the same order of magnitude over approximately the same time range.

Comment

After intraperitoneal injections γ-globulin appears in the blood stream in minutes [7] and persists for a measurable length of time. Using I^{131}-labeled globulin, Dixon [8]

TABLE 3.—*Summary of the Significance of Treatment*

	Series 1-4 * (40 Eyes)		Series 5 † (16 Eyes)	
Day	χ^2	P	χ^2	P
1	0.53	0.46	0.00	1.00
2	2.11	0.15	0.00	1.00
3	1.02	0.31	0.00	1.00
4	1.02	0.31	1.07	0.30
5	4.44	0.03	3.69	0.05
6	4.33	0.04	3.69	0.05
7	4.33	0.04	5.33	0.02
8	5.63	0.02	2.62	0.10
9	2.13	0.14	4.27	0.04
10	1.13	0.29	2.29	0.13
11	0.48	0.49	2.29	0.13
12	0.48	0.49	2.29	0.13
13	0.96	0.33	1.00	0.32
14	1.66	0.20	1.00	0.32

* Half the animals were pretreated with parenteral human γ-globulin 24 hours prior to inoculation of herpes simplex.
† Half the animals were treated with parenteral human γ-globulin three days after the inoculation of herpes simplex.

found the half-life of foreign globulin in the blood stream of rabbits to be four to five days.

As reviewed by Woods,[9] in 1933, Leber showed that agglutinins were present in the aqueous of passively immunized animals about 4 hours after the passive immunization and apparently reached their highest concentration in about 24 hours. Miyaschita, Grüter, and Salus showed that agglutinins were present in aqueous at 1/1000 to 1/2000 of the serum level. In 1909 Miyaschita showed that after a puncture of the anterior chamber the secondary aqueous contained antibody levels augmented 200 to 800 times. Kodoma showed that repeated punctures of the anterior chamber raised aqueous levels to 12% to 25% of the serum level.

Davson,[10] in his more recent work, states that the normal blood-aqueous barrier is penetrated by the various substances in the plasma at a characteristic rate. The very slowly penetrating substances of the plasma, the high-molecular-weight proteins, are present in such small concentrations that their presence is detected only with difficulty; the aqueous is frequently described as virtually protein-free. To show that normal conditions prevailed in this experiment a formol gel test for globulin was performed on pooled samples of primary aqueous withdrawn from our rabbits at the time of inoculation, i. e., 24 hours after the intraperitoneal injection of 5 cc. of γ-globulin. The negative results indicated that the barrier was still intact.

To study the effect of the inoculation procedure we withdrew 0.04 cc. and replaced 0.03 cc. of aqueous. Samples of secondary aqueous were withdrawn two hours later and subjected to a formol gel test. This time the reaction was positive, indicating that the barrier had been broken.

We assume, therefore, that human globulin was present in the aqueous humor starting from the time of inoculation of the virus. Nonetheless, infection not only occurred in the pretreated animals but continued unmodified until the fifth day after inoculation of the virus. When immune globulin was withheld until the third day of the disease, significant modification likewise appeared on the fifth day, exactly as in the case of the pretreated animals. One may, therefore, hypothecate that the virus became fixed to tissue before it could be neutralized by antibody and that the modification of the disease resulted from phenomena occurring in the tissues after development of the infection.

Since it is generally believed that intracellular virus is protected from the action of extracellular antibody, any modification of disease already developed must result after breakdown of tissue cells, a process which would liberate the virus from the cells or permit penetration of the globulin into decomposing cells. Similarity of results in the pretreated and post-treated animals could be explained by postulating that sufficient time for the breakdown of tissue cells must elapse before the virus is exposed to antibody which has accumulated in the aqueous and iris stroma as a result of increased capillary permeability and inflammatory hyperemia.

Such a hypothesis is also consistent with the failure of corneal infections to respond to immunotherapy. In the corneal epithelium, a layer of high cellularity and low vascularity, spread of virus from cell to cell could (and probably does) occur without risk of interception by extracellular antibody. In the corneal stroma, a layer of low cellularity and low vascularity, it is possible that the concentration of antibody would be insufficient to prevent infection of the corneal stroma cells by virus liberated from the overlying epithelium, if, in fact, such infection actually does occur. Pathologic vascularization of the cornea, by increasing the concentration of antibody, could conceivably shift the balance in favor of the immune mechanism.

The fact that significant differences are no longer found after the eighth day is explained by spontaneous improvement of untreated eyes in the experimental disease.

In experiments of this type, the most sensitive test of therapeutic effect requires a dose producing infection in only 50% of eyes inoculated (ID_{50}). An infectious dose which gives a marked reaction in 100% of eyes constitutes a more serious challenge to the therapeutic effect of an agent being tested, and we therefore feel that this adds significance to our findings.

General Comment

Although signs of iris irritation (miosis, circumcorneal congestion, and photophobia) occur in the majority of human cases of herpes corneae, it is problematic how many of these represent actual infection of the iris and ciliary body by the virus. Presumably, the manifestations in many of these cases can be attributed to axonal reflexes arising in the diseased cornea. In others, however, the occurrence of iris edema, ciliary hyperemia, and secondary glaucoma suggests that the anterior uvea may be the site of active involvement by the virus. The present experiments, in addition to the clinical impressions received from a limited number of cases,[11] suggest that the parenteral use of human serum γ-globulin represents a rational and innocuous, if not definitive, approach to the difficult therapeutic problem presented by certain cases of herpes simplex infection in the human eye.

Summary and Conclusions

Inoculation of herpes simplex virus into the anterior chamber of rabbits produced a specific inflammation of the anterior uveal tract.

The course of experimental herpetic iritis was shortened by human serum γ-globulin, injected intraperitoneally either one day before or three days after inoculation.

Theoretical aspects of the problem are discussed.

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Thermal Detachment of the Anterior Lamella of the Anterior Lens Capsule

A Clinical and Histopathologic Study

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Exfoliation of portions of the anterior lens capsule from the effect of heat was recognized and studied extensively by Ascher,[1] Elschnig,[2] Vogt,[3] and other European investigators 35 years ago. For about 10 years thereafter reports in the European literature on various aspects of this condition appeared frequently, but they have been scarce since then. The condition is probably appearing less often because of less exposure to heat in the modern manufacture of steel and glass and because of better protection of eyes with filters. Although heat cataract, which begins at the posterior pole of the lens, and detachment of the anterior lamellae of the anterior capsule may be associated, either may appear independently as a separate clinical entity. Vogt and his co-workers and other investigators have shown that heat cataract is produced by infrared rays and may occur without detachment of the lens capsule.

Capsular exfoliation is typically bilateral. The anterior capsule is affected within the pupillary region. The edge of the detachment lies peripherally, behind the iris. The rupture of the capsule occurs approximately concentric with the pupil, and the free edges of the central flap curl forward.

Senescence as well as the application of heat can bring about loosening and dissociation of the anterior capsular lamellae within the living eye, and both in heat detachment and in senile exfoliation a dissociation of the capsule into coarse single lamellae precedes the detachment. Among those working with high concentrations of heat who are equally or similarly exposed, detachment of the lamella occurs in only a few, indicating an individual predisposition.

Vogt suggested that the separation of the lamella is probably a consequence of the total damage of the heat of convection which is produced in the iris and lens by these rays. Goldschmidt [4] believed from his study of several cases that the entire thickness of the capsule and the underlying epithelium are damaged and suggested that the infrared rays slowly coagulated the surface of the lens, rendering the cortex impervious to the action of the aqueous and thereby preventing the formation of a traumatic cataract. Riedl [5] studied two enucleated eyes with the lens in situ, in which detachment of the lamina had ocurred, and described the increased tendency to fissure formation and the fragility of the capsule.

It was anticipated that, in examining workers from the iron industry, heat cataracts and detachment of the anterior capsular lamellae might be observed frequently. Such has not been the case, and only one patient with true exfoliation has been seen in 10 years. Death of this patient presented an opportunity for direct correlation of the clinical and histopathologic findings of this condition.

Report of a Case

CASE 1.—A man, aged 72, was first examined in October, 1949, suffering from agonizing pain and loss of vision in the left eye. The pain had been developing with increasing severity for three weeks,

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and miotics prescribed elsewhere had been ineffectual. Diminution of left vision had been first noted three years previously, and at that time a diagnosis of cataract had been made. There were no complaints about the right eye.

For 31 years he had been welding steel for railroad car axles, working eight hours a day, six days a week. He was at a 3 ft. working distance from the steel, which was at an average temperature of 1800 to 2200 F. At no time during this work did he wear a shield or a filtered lens. For the past 12 years he had been working intermittently in a blacksmith shop, with temperature of the working metal around 1400 F, and protective lenses were not used.

He was a well-developed well-nourished white man, whose blood pressure was 200/105. The presence of diabetes had been discovered at the age of 69, and at the time of examination (three years later) the patient required 100 units of insulin daily.

Examination: In the right eye visual acuity was 20/25. Upon dilation of the iris, a rupture of the lamella of the anterior capsule of the lens could be seen as a delicate rectangular flap of homogeneous material, approximately in the center of the pupil, floating in the aqueous humor (Fig. 1). With a narrow slit-lamp beam of light at a 45-degree angle, the glistening outlines could be thrown into relief. The rectangular flap was free below and on two sides but remained attached at its base above. As they curled upward, the free edges glistened in front of the lens, which was slate-blue. Scattered over the anterior capsule both in the detached and in the nondetached areas were small dark-reddish-brown clumps of pigment. Posterior to the detached area the lens was covered by a thin bluish-white membranous layer, apparently capsular in nature, beneath which the lens showed only the changes of nuclear sclerosis customarily observed at this age. There were no subcapsular deposits posteriorly and no indications of senile or thermal cataract. The ocular tension was 28 mm. Hg. The visual field was normal. The angle was open, but a few peripheral anterior synechiae were present, and a diagnosis of open-angle glaucoma was made.

In the left eye vision was nil. The ciliary injection was intense; the anterior chamber, shallow, and seclusio pupillae was present. The corneal bedewing was so severe that most of the details of the iris, lens, and capsule were obscured. There were a few scattered keratic precipitates and a heavy aqueous flare with cells. The ocular tension was 75 mm. Hg.

Enucleation of the left eye was urged because of the presence of absolute glaucoma with pain and the possibility of an intraocular tumor. However, the patient and his relatives insisted upon an operation for the relief of glaucoma, as that had been the diagnosis elsewhere. On the next day, with use of thiopental (Pentothal) sodium anesthesia, a wide basal iridectomy with a 2 by 4 mm. sclerotomy was performed, but only about 0.5 cc. of aqueous trickled out, and the eye remained firm. A 1.5 mm. trephine opening was then made in the upper outer quadrant of the sclera, 8 mm. posterior to the limbus. On penetration of the sclera about 2 cc. of greenish-brown fluid gushed forth. The tension was lowered immediately, and the anterior chamber filled with blood. In a few minutes the eye became firm again, owing to intraocular hemorrhage.

The operation was temporarily halted, and another consultation was held with the patient's relatives, at which time permission for enucleation was again urged. Acquiescence was secured, and the enucleation was performed. The Armed Forces Institute of Pathology report is as follows: "Malignant melanoma of choroid, spindle cell subtype A; massive intraocular hemorrhage with retinal detachment; secondary glaucoma, (depression of lamina cribosa); atrophy of optic nerve; cataract, senile type; lens capsule suggestive of lens exfoliation."

During the postoperative period and afterward, glaucoma of the right eye was observed. Pilocarpine nitrate (2%) was

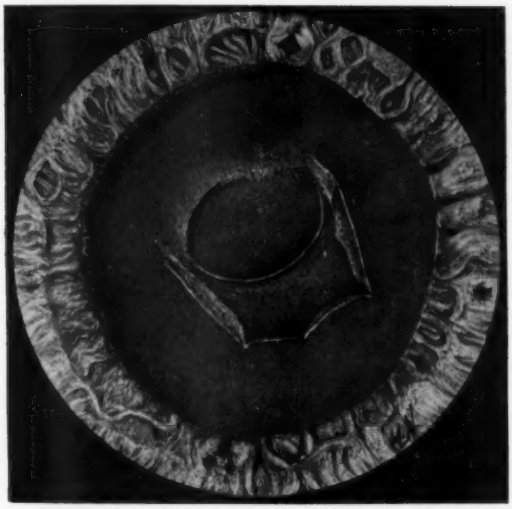

Fig. 1 (Case 1).—Clinical picture of right eye one year prior to basal iridectomy. The rectangular flap is the detached anterior capsular lamellae, its free edges rolled up like a scroll. The thin gray line indicates the region of spatial separation of the membrane from the remaining lens capsule. The broad gray area above it indicates the site of incipient dissociation and probably wrinkling (see Fig. 2).

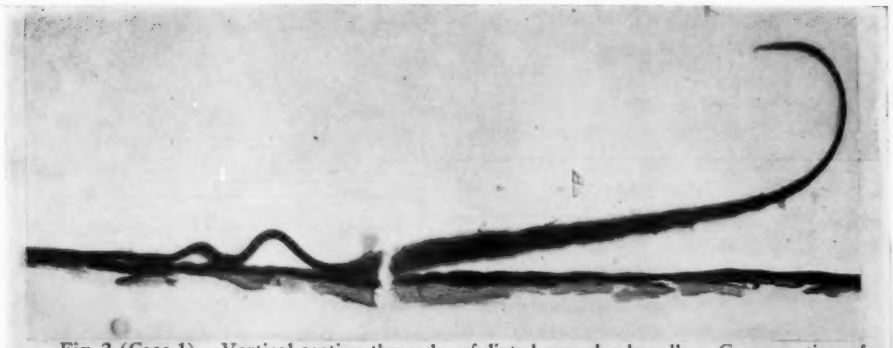

Fig. 2 (Case 1).—Vertical section through exfoliated capsular lamellae. Cross section of several horizontal folds. Note blue color of capsule and red color of detached membrane. Trichrome stain; × 115.

Fig. 3 (Case 1).—Area in anterior capsule near the point of beginning dissociation. Note the different staining properties of degenerating anterior lamellae and remaining capsule and the irregular spacing of capsular epithelial cells. Hematoxylin and eosin; × 300.

Fig. 4 (Case 1).—Anterior equatorial region of the lens capsule, showing distinct pericapsular membrane (zonular lamella) with the same staining property as the capsule. Trichrome stain; × 560.

instilled three times a day, but the tension was not controlled. Physostigmine (Eserine) sulfate (¼%) was used, but the ocular pressure remained at 32 mm. Hg. Phenylephrine (Neo-Synephrine) hydrochloride (10%) reduced the ocular tension to 17 mm. Hg, and by use of it three to four times a day ocular tension was controlled satisfactorily for five weeks.

By late December the tension became elevated again, despite the increased use of phenylephrine, and in January, 1950, the patient was hospitalized and a full iridectomy was performed. The iris prolapsed after the keratome incision was made, so that it was unnecessary to introduce the forceps into the anterior chamber to grasp the iris. The iris sector was torn away from its root and sectioned. The detached lamella was not touched, and postoperatively it remained unchanged in size and shape. The ocular tension remained within normal limits for three months, but by April, 1950, it increased again to 32 mm. Hg. Pilocarpine nitrate (2%) was again ineffective, but the tension was controlled with the combination of carbachol (Carcholin) and phenylephrine. Early in 1951 the visual acuity was 20/25. The central visual field was normal. By the middle of 1951 a senile cataract had begun to form, and by December the vision had decreased to 20/50. The ocular tension remained within normal limits with the use of carbachol and phenylephrine, and by the middle of 1953 the cataract had progressed further, so that the vision was 20/200. The patient's general health had become poor. The fundus details could not be seen clearly, but retinal aneurysms were thought to be developing.

By October, 1954, the vision had decreased to counting fingers and projection was not present in all fields. His diabetes was not well controlled. The ocular tension was 24 mm. Hg. In July, 1956, the tension was 27 mm. Hg and the vision was limited to light perception, and projection in some fields. The splitting of the anterior lens capsule appeared to be identical with its appearance when the patient was first examined, seven years previously. In November, 1956, the patient died, and the eye was obtained for study.

Histologic Findings.—The eye was sectioned in the vertical plane to show, if possible, the transition of the detached lamella into the intact lens capsule.

Behind the superior limbus there was a slanting well-healed penetrating scar, whose course was marked by some inclusions of pigment and whose inner end was indicated by a slight thickening of Descemet's membrane.

The corneal epithelium was slightly irregular, owing to hydrops of some of its foot cells. Stroma and endothelium appeared normal aside from some hydrops of the latter in the most peripheral region over small Hassall-Henle warts.

The anterior chamber was normally deep; the angle was open except above, where the stump of iris root was lying, apparently loosely, against the trabeculum or portions of it. The spaces of Fontana were densely packed with pigment debris, and most of the trabecular meshwork appeared sclerosed (Fig. 5).

The chamber angle and ciliary body had hyperopic configuration. A wide portion of the superior iris was missing (total postoperative coloboma). There was a broad old posterior synechia of the pupillary portion of the inferior iris with some hyalinized fibrous tissue extending a short distance from the pupillary border onto the anterior surface of the lens. The middle and peripheral portions of the iris contained some scattered lymphocytes but were otherwise normal.

There was some hyalinization of the ciliary processes and some lymphocytic infiltration in the ciliary body. The choroid revealed scattered drusen formation in the equatorial region. At one place there was a circumscribed detachment of the pigment epithelium by serum and hemorrhage. There were

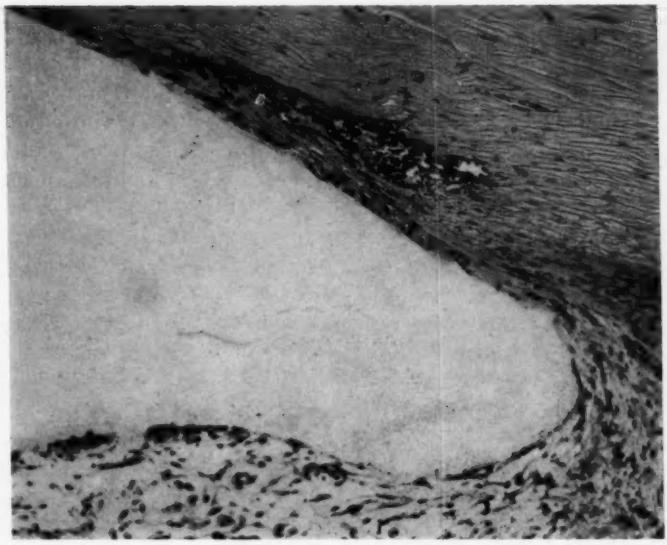

Fig. 5 (Case 1).—Open chamber angle, pigment debris in spaces of Fontana and canal of Schlemm, sclerosis of trabecular fibers; reduced to approximately 87% of mag. × 125.

no visible pathologic changes in the underlying choroid.

The retina showed extensive peripheral cystic degeneration. Within the superior temporal sector there was almost complete disappearance of the ganglion cells, excepting a few immediately adjacent to some arterioles. This loss of ganglion cells began abruptly in the center of the macula, whose upper half, including the fovea, was flat and whose lower half had approximately normal appearance. The region of the fovea centralis was replaced by glial tissue which contained a few groups of pigment-laden phagocytes.

There was marked narrowing of the lumen and hyalinization of the walls of the superior temporal artery—changes which became more marked after division of this branch into several arterioles, one of which was completely occluded. The outer layers of the superior temporal retina were well preserved except over the circumscribed detachment of the pigment epithelium described above. There, only the inner nuclear layer was preserved.

There was partial atrophy with some secondary glial proliferation of the superior half of the optic nerve. The cribriform plate was in situ.

The lens. The lens in the sections measured 9.0×4.5 mm. at its largest diameters.

The most striking alteration was a splitting of the anterior capsule, producing a membrane whose nasal, inferior, and part of its temporal borders floated freely in the anterior chamber (Fig. 2). Its inferior border was slightly rolled outward. Above, this membrane merged with the capsule of the lens, but for an extensive stretch beyond this point of junction a dissociation of the anterior capsular lamellae was indicated by the different staining properties of the superficial exfoliating layers and the deep lamellae (Fig. 3). This difference was visible even with the hematoxylin-and-eosin stain but was especially striking with Masson's trichrome stain, which showed the degenerated portion of the capsule a reddish pink against the bright blue of the collagen fibrils of the normal portion (Fig. 2).

Some distance before the actual separation, the degenerating lamella was wrinkled and there were at least three cross sections of large horizontal folds demonstrable, indicating that the connection between the exfoliating lamella and the remaining lens

capsule was rather loose, especially approaching the site of detachment. The site of the beginning visible dissociation of the two portions of the lens capsule would have corresponded approximately to the pupillary border of the portion of iris which was removed surgically.

There was no scattering of small shreds and pieces of degenerating capsular substance anywhere. The insertion of the zonular fibers in the anterior and posterior equatorial regions was undisturbed, and there were no pathologic staining properties of the pericapsular membrane (Fig. 4).

In the periphery the epithelial cells of the lens had approximately normal cubical shape and were evenly spaced. Approaching the anterior polar region they became flatter and the layer lost its continuity in many places by irregular gaps. Most of the lens cortex had fallen out during preparation of the specimen, but remnants still present showed globular disintegration, lamellar separation, and irregularities of the equatorial nuclear bow.

Histochemical Study.—The change in the histochemical properties of the exfoliated portion was brought out well by the Rinehart [6] modification of Hale's colloidal iron stain for acid mucopolysaccharides and by the periodic acid-Schiff stain.

The latter gave an intense coloring of the undetached portion of the capsule, in contrast to the pale reddish hue of the detached membrane.

According to Gomori,[7] elastic fibers in certain locations contain an unidentified nonlipid substance which gives a positive aldehyde reaction, such as the inner elastic coat of small arteries and also, apparently, Descemet's membrane, the outer half of Bruch's membrane, and the lens capsule. The relative loss of staining property of the exfoliated portion of the lens capsule with this stain may simply be an indication of the degeneration of the fibrillar constituents of the membrane.

Rinehart's stain, on the other hand, was more suggestive of damage to the cement substance. The relatively normal in situ portion of the lens capsule was stained a buff color similar to that of Descemet's membrane, a shade which is indicative of mucoproteins or glycoproteins, substances which are present in the cement substance between the submicroscopic fibrillar elements of these elastic membranes.

In contrast, the detached membrane stained blue, a color which was paled but not completely removed by hyaluronidase. The reason for this behavior of the degenerated membrane is not clear; the loss of the normal buff color, however, points to the destruction of the cement substance.

The pericapsular membrane and the zonular elements entering it also stained a brilliant blue with this method. This staining property which they shared with the exfoliated membrane should not be taken as proof of an intimate relationship of these structures. While the blue stain of the detached lamellae cannot be interpreted with our present knowledge, the known presence of abundant hyaluronic acid in the zonule, which is developmentally part of the vitreous, fully explains its histochemical reaction.

Ungar [8] and others have found an increase of proteolytic activity after thermal injury to tissues and believe that this proteolysis is at least partly caused by activation of an enzyme system present in normal blood and tissue as an inactive precursor.

While the avascular lens capsule cannot be closely compared to the experimental tissues used by these authors, such as skin and lung parenchyma, the interfibrillary cement substance could contain such an inactive enzyme precursor whose gradual activation might bring about proteolysis within the cement substance and thus loosening of the lamellae and eventual exfoliation. There is, of course, complete lack of repair or inflammatory response to the thermal injury of this avascular, defenseless structure, and the histopathologic and histochemical picture confronting one is that of pure, unrepaired degeneration.

Measurements.—The exfoliated portion of the lens capsule at its thickest was twice the width of the remaining capsule under it. A greater thickness of the detached membrane was simulated in places by a tangential section of one of its folds. The main measurements of the lens capsule and the degenerating lamellae are as follows: (1) lens capsule just in front of equator, 20μ; (2) anterior lens capsule 3 mm. from equator, 16μ; (3) lens capsule at anterior pole, 6μ; (4) at the point where two zones with different staining property appeared, 16μ, of which 10μ belonged to the unaltered lens capsule and 6μ to the superficial degenerating lamellae; (5) at the point of spatial separation, the detached membrane was 16μ and the underlying capsule, 6μ; the fibrillae of the detaching membrane may have been slightly drawn apart at this place, producing the measurement of 16μ as compared with 14μ as the thickest portion of the exfoliated membrane elsewhere; (6) posterior lens capsule at the posterior pole, 2.5μ.

Comment

The degeneration of the anterior lens capsule so beautifully shown in its entire continuity in the vertical sections of this specimen seems to have little or no connection with the zonular lamella. Within the vulnerable pupillary region two-thirds of the capsule was affected, and in this area the damage had extended also to the capsular epithelium. The striation of the zonular lamella, on the other hand, could be followed from the equatorial region toward the anterior pole for a considerable distance but not quite to the point of dissociation of the degenerating lamellae. The pericapsular membrane, even at its thickest, in the equatorial region, was less than half the thickness of the exfoliated capsular membrane.

In the interpretation of the glaucoma the most significant findings are the sclerosed trabeculum and the open angle of the anterior chamber, which suggest the primary, deep chamber type, entirely unconnected with the capsular degeneration of the lens.

Another remote possibility is a simultaneous damage to the lens capsule, capsular epithelium, and pars iridica retinae by the heat of convection generated in the lens and the stroma of the iris and subsequent blocking of the spaces of Fontana by pigment. No definite information could be gained from the histologic sections as to the exact time when the complete obstruction of the trabecular region by pigment occurred, but marked pigment dispersion had already been mentioned in the description of the clinical picture prior to the surgical procedure.

Some confusion exists in the literature, as Theobald[9] has pointed out, concerning the cases of true exfoliation of the lens capsule, in which a coherent membrane splits away from the posterior layers of the anterior capsule, rolling up like a scroll, and pseudoexfoliation. The term pseudoexfoliation was appropriately chosen by Theobald for a histopathologic picture which consists of flocculi and membranes of accretions of an unknown substance deposited on the free surfaces of anterior and posterior chambers. The clinical counterpart of this condition leads almost invariably to glaucoma and is known in the literature as glaucoma capsulare.

A juxtaposition of some of the histologic details of true exfoliation and of pseudoexfoliation in this article will reemphasize the essential difference between these two conditions.

Case 2.—A man 71 years of age complained of having had failing right vision for two years. For the previous year there had been frequent attacks of pain and redness in this eye. The left vision had been failing for three months.

The right vision was nil; the right eye was stony hard, and corneal degeneration prevented a clear view of the deeper structures. The left vision was 20/100; the left bulb was pale; the tension, 18.0 mm. Hg (Schiøtz). After dilatation of the pupil a

Fig. 6 (Case 2).—Feathery deposits attached to anterior equatorial region of pericapsular membrane in pseudoexfoliation. Compare smooth surface of same region in Case 1, of true exfoliation, in Figure 4; × 265.

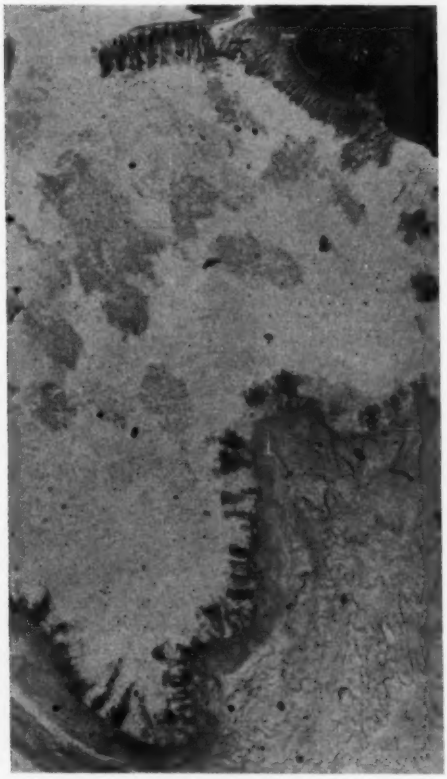

Fig. 7 (Case 2).—Arborescent accretions of pseudoexfoliation clinging to ciliary processes, zonular fibers, and anterior surface of vitreous; × 125.

faint grayish disc in the anterior lens capsule became visible. Numerous grayish-blue flocculi were fastened to the pupillary border and in some places to the outline of the capsular opacity. A diagnosis of senile "desquamation" of the lens capsule and of probable glaucoma lenticulocapsulare in the other eye was made.

The details in Figures 6, 7, and 8 illustrate some of the findings in the enucleated right eye of this patient. A carpet of arborescent deposits covered extensive areas of the ciliary epithelium, the anterior vitreous, the zonular fibers, and the lens capsule. It was interesting to see how these accretions were attached in some places to two surfaces, for instance vitreous and ciliary process (Fig. 8), slightly deforming at least one of the surfaces, suggesting a powerfully adhesive quality.

Note for contrast with Figure 6 the clean-cut surface of the anterior equatorial region of the lens in the eye with the true exfoliation (Fig. 4).

Summary

A direct correlation is made of the clinical and histopathologic findings in an eye with true exfoliation of the lens capsule due to thermal injury.

Fig. 8 (Case 2).—Accretions of pseudoexfoliation connecting anterior vitreal surface and ciliary process, demonstrating marked adhesive quality of deposits; × 265.

Histochemical tests suggested damage predominantly to the interfibrillary cement substance.

Findings in an eye with pseudoexfoliation are briefly contrasted with those of the true exfoliation.

The drawing (Fig. 1) was done by Mrs. Mary Nicholl Burnham.

903 S. 21st St. (5).

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Comparative Studies on Anesthetic Properties of Primacaine HCl

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This paper presents the results of clinical and experimental work comparing a new local anesthetic agent, 2′-diethylaminoethyl 2-butoxy-3-aminobenzoate (Primacaine) hydrochloride * to certain other local anesthetics in common use, particularly from the standpoint of duration of effect. It is the third paper from our department reporting work started in 1951 in an attempt to find a local anesthetic of sufficient duration to avoid the period of acute postoperative pain which occurs during the first few hours after ocular surgery.[1,2] Primacaine hydrochloride was recently made available to us as a local anesthetic agent. It has low toxicity, great potency, and a somewhat longer duration than other anesthetics currently available.[3,4]

Scheie et al.,[1] in 1952, reviewed the literature on long-lasting local anesthetics and pointed out the advantages which would accrue from local anesthesia of sufficient duration to avoid postoperative pain in ocular surgery. Much restlessness, nausea, and vomiting, all of which can be aggravated by sedatives and analgesics, would be avoided, and the general welfare of the patient would be greatly enhanced. Rather extensive observations of patients after ocular surgery showed that the period of most excruciating pain begins within 1 to 2 hours and disappears 8 to 10 hours following operation. After that length of time pain is insignificant. A local anesthetic, therefore, which would remain effective for 8 to 10 hours would prevent the major portion of postoperative discomfort.

Two long-lasting local anesthetics which were available at that time were investigated: A preparation containing procaine, procaine hydrochloride, and butyl-*p*-aminobenzoate (Efocaine) caused such severe reaction at the site of its injection that its use was concluded to be contraindicated. Another local anesthetic agent, U-0045 (bis-[β-(*o*-methoxyphenyl)-isopropyl]-amine), was made available for experimental use (Upjohn). This was very satisfactory for retrobulbar anesthesia; 1 cc. of 0.15% U-0045 combined with 1 cc. of 2% procaine HCl (0.12% U-0045) gave excellent anesthesia which persisted for 8 to 12 hours. Nearly all postoperative pain was prevented, and no complications were encountered in more than 600 operations. However, experimental observation showed that solutions stronger than 0.2% caused some local tissue irritation when injected intracutaneously or into the anterior chamber of the rabbit eye,[5] and for that reason it has not and probably will not be made available commercially.

Stimulated by the gratifying results from the use of U-0045 in eliminating postoperative pain, which emphasized the need of a long-lasting local anesthetic agent, attempts were made to prolong the effect of available agents. Scheie,[2] in 1955, reported a method of maintaining continuous retrobulbar anesthesia by repeated injections of local anesthetic solution through a fine polyethylene tube, one end of which rested in the muscle cone. A specially made thin-walled No. 19

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Fig. 1. — Polyethylene tubing extending from muscle cone attached to chamber which is sutured to the skin at the preauricular area.

gauge needle is inserted into the muscle cone for retrobulbar anesthesia, and anesthetic solution is injected. The syringe, then, is removed from the needle, which remains in place, and a 5 in. length of polyethylene tubing, P. E. 10 gauge, is threaded through the needle into the muscle cone. The tubing is supported in the muscle cone while the needle is withdrawn over it. The free end of the tubing is then connected to an adaptor leading to a chamber, made of ordinary intravenous tubing, containing anesthetic solution (Fig. 1). Postoperatively, when the effect of the anesthetic solution wears off and the patient complains of pain, more anesthetic solution is injected into the muscle cone through the wall of the intravenous tubing, after it is first sponged with alcohol. A 2 cc. syringe with a No. 27 needle is used. This can be repeated as many times as it may be needed. The method has been safely used in more than 700 patients and has proved practical in eliminating postoperative pain without the use of analgesic or sedative drugs. The method is also of value for the relief of pain in acute congestive glaucoma and in persons for whom repeated manipulations, such as paracentesis; may be indicated over a period of several days. The tubing is usually removed at the first dressing, 18 to 24 hours after operation.

The retained polyethylene tube technique has been used in the present study for the clinical evaluation of procaine HCl, lidocaine HCl, and Primacaine HCl. The duration and effectiveness of these local anesthetic agents was determined by recording the time after operation at which the patient complained of pain and by noting the number of times injection of anesthetic solution was required.

Primacaine HCl was synthesized and the properties were studied by Epstein and Meyer.[3,4] It is being used at present rather widely for dental surgery and is commercially available for this purpose.† Studies are also under way, on an experimental basis, to determine its value in various other fields of surgery. Primacaine differs from procaine in that the amino group on the benzene ring is in the meta instead of the para position and a butoxy group has been added to the 2 position (Fig. 2). Experimental work by Epstein et al.[3,4] has indicated that Primacaine HCl is a more potent and less toxic anesthetic agent than procaine HCl. The duration of anesthesia is about two and a half to three hours. Reports of its clinical use in dental surgery are beginning to appear in the literature. Monheim [6]

† Approved by the Department of Health, Education, and Welfare, Food and Drug Administration, for use as a dental anesthetic, Nov. 19, 1954.

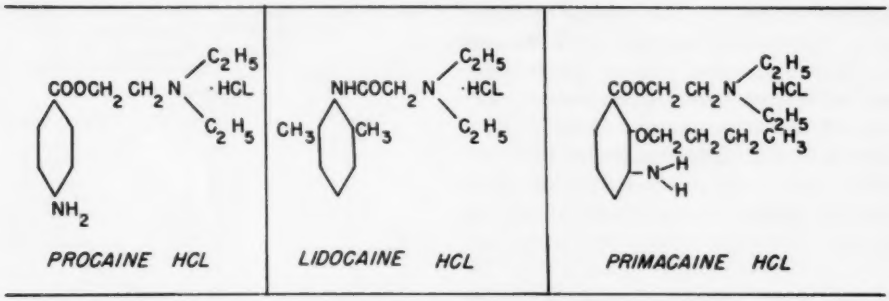

Fig. 2.—Chemical structure of procaine hydrochloride, β-diethylaminoethyl *p*-aminobenzoate HCl; lidocaine hydrochloride, α-diethylamino-2,6-acetoxylidide HCl, and Primacaine hydrochloride, 2′-diethylaminoethyl 2-butoxy-3-aminobenzoate HCl.

has used it for infiltration and for mandibular, infraorbital, and tuberosity block anesthesia in 470 patients. Rogers [7] has used it in 300 patients. Both observers reported prompt and profound anesthesia. No evidence of toxicity was encountered nor were any allergic manifestations noted, even in patients who received injections in spite of a history of allergic response to other anesthetic agents. Both workers concluded that Primacaine HCl is an excellent anesthetic. Monheim also gathered data from 15 dental schools where Primacaine HCl had been used for clinic work. A total of 3016 injections had been given to 2700 patients. These data also revealed absence of toxicity, excellent anesthesia, and lack of postinjection reactions.

Primacaine HCl was first made available to us for ocular surgery in June, 1956. We incorporated it in our study of local anesthetic agents already under way, and since that time we have used it for both experimental and clinical purposes, comparing it with procaine HCl, lidocaine HCl, tetracaine HCl, and certain other substances.

I. Duration of Retrobulbar Anesthesia in Rabbits

Our first experimental studies consisted of comparing the duration of action of retrobulbar injections of Primacaine HCl, 1.5% with and without hyaluronidase, with that of tetracaine HCl, 0.1%, lidocaine HCl, 1.0%, and procaine HCl, 2.0%, in rabbits (Table 1). A block was considered to be successful when the pupil of the injected eye became widely dilated and fixed to light. We found in our previous study [1] that evaluation of the pupillary light reaction is a more reliable sign of block of the ciliary nerves and ganglion in animals than testing for corneal anesthesia. Retrobulbar anesthesia was obtained in 10 eyes by use of local anesthetic solutions without hyaluroni-

TABLE 1.—*Duration of Anesthesia* *

Eye	Duration, Min.							
	Tetracaine 0.1%	Tetracaine 0.1%+ Hyaluronidase	Procaine HCl 2.0%	Procaine HCl 2.0%+ Hyaluronidase	Lidocaine 1.0%	Lidocaine 1.0%+ Hyaluronidase	Primacaine 1.5%	Primacaine 1.5%+ Hyaluronidase
1	75	60	60	45	15	30	100	40
2	105	105	105	45	60	30	100	70
3	105	45	45	30	30	60	95	65
4	45	30	90	30	60	75	100	50
5	75	105	45	15	45	45	80	45
6	75	60	45	45	45	30	95	60
7	120	105	45	30	60	30	80	60
8	90	90	30	45	45	45	75	60
9	30	45	135	60	60	60	100	75
10	105	105	45	30	30	30	115	70
Av.	82	75	61	37	45	43	95	60

* Retrobulbar injection of 0.5 cc. anesthetic solution in rabbits.

dase and in 10 eyes with use of hyaluronidase. The average duration of Primacaine HCl was 95 minutes without hyaluronidase and 60 minutes with hyaluronidase. This was approximately the same as that of tetracaine HCl and somewhat longer than lidocaine HCl or procaine HCl. No undue reaction occurred as a result of the injections.

II. Local Irritation

A. Anterior Chamber Injection in Rabbits.—Primacaine HCl, 1.5%, was injected into the anterior chamber of rabbit eyes to determine its local tissue irritation. This test for irritative properties of local anesthetic agents has previously been described by Spencer, Scheie, and Dripps.[5] Procaine HCl and tetracaine HCl were found to cause no irritation when injected into the anterior chamber. Lidocaine HCl caused very slight reaction. Primacaine HCl injected into the anterior chamber of 10 eyes caused no reaction, being comparable to sodium chloride, procaine HCl, and tetracaine HCl (Table 2). Epstein, using other tests, also found it to be nonirritant.

B. Conjunctival Instillation.—Conjunctival instillation of 1.5% Primacaine HCl caused slightly less discomfort than tetracaine HCl, 1.0%. No staining with fluorescin resulted. Poor anesthesia was produced, and the duration was only 5 to 10 minutes (Table 3).

TABLE 2.—*Average Corneal Haze and Circumcorneal Injection Produced by the Anterior Chamber Injection of Local Anesthetic Solution* *

	Conc., %	Haze and Injection
Primacaine HCl	1.5	
Dibucaine HCl	0.1	0 or less
Tetracaine HCl	0.8	than 1
Procaine HCl	0.8	
Piperocaine HCl	Ringer's	
Lidocaine HCl	0.1	1
Hexylcaine HCl	0.15	3-4
Pyrrolocaine HCl (β-pyrrolidinoethyl *p*-*n*-propoxybenzoate)	0.8	
U-0045 lactate (bis-[β-(o-methoxyphenyl)-isopropyl]amine)	0.8	4
A-2011 HCl (β-diethylaminoethyl 2,3,5,6-tetramethylbenzoate)	0.8	

* Ten rabbits in each group.

TABLE 3.—*Duration of Corneal Anesthesia After Conjunctival Instillation*
Clinical Study

	Objective Recovery, Min.	
Patients	1.0% Tetracaine	1.5% Primacaine
1	25	5
2	25	5
3	25	7
4	25	7
5	25	8
6	30	7
7	40	6
8	20	6
9	60	5
10	30	5
11	20	7
12	30	7
13	30	3
14	30	3
15	30	5
16	30	6
Av. duration	30	6

III. Anesthetic Qualities

A. Degree of Anesthesia.—The adequacy of anesthesia produced by procaine HCl, lidocaine HCl, and Primacaine HCl was compared in approximately 600 ocular operations of various types. All produced excellent anesthesia. Retrobulbar anesthesia produced by the injection of lidocaine HCl and Primacaine HCl was slightly delayed compared with that of procaine HCl. The lag was a matter of 30 to 60 seconds. This was best evaluated in repeat injections for the relief of pain with use of the polyethylene tubing method. Procaine HCl relieved pain almost instantaneously, whereas the above length of time was required for lidocaine HCl and Primacaine HCl. No evidence of toxicity or local irritation was noted from any of these anesthetic agents.

B. Duration of Retrobulbar Anesthesia.

Observations were made as to the duration of retrobulbar anesthesia with use of procaine HCl for 188 eyes, lidocaine HCl for 149 eyes, and Primacaine HCl for 264 eyes. All patients had received the same preoperative medication, consisting of chlorpromazine, 25 mg. the night before and two times the morning prior to the operation. Pentobarbital (Nembutal), 0.1 gm., was given one hour before surgery. The time was noted at which the patient first complained of postoperative pain in various operative procedures (Table 4). The average was 3 hours 20 minutes following cata-

TABLE 4.—*Continuous Retrobulbar Anesthesia Retained Polyethylene Tube Technique*

	Av. Time of Onset of Pain	Injections for Relief of Pain	Eyes Operated on, No.
Procaine			
Cataract extraction	3 hr. 20 min.	3	141
Retinal detachment	2 54	3	15
Corneal transplant	2 50	2	7
Elliot trephine	2 45	1	3
Iridencleisis	3 12	2	10
Enucleation	3 30	1	2
Evisceration	2 30	2	6
Strabismus	3 10	1	3
Cyclodiathermy	3	1	1
			Total, 188
Lidocaine			
Cataract extraction	3 20	2	103
Retinal detachment	2 35	3	16
Corneal transplant	4 12	3	6
Elliot trephine	3 56	1	6
Iridencleisis	2 22	2	7
Enucleation	3 42	2	5
Strabismus	1 20	3	3
Cyclodiathermy	4 45	1	1
Removal of intraocular foreign body	No postop. pain		1
Freeing of anterior synechiae	No postop. pain		1
			Total, 149
Primacaine			
Cataract extraction	4 25	1	203
Retinal detachment	4 12	2	25
Corneal transplant	6	2	7
Elliot trephine	5 15	1	4
Iridencleisis	3	2	2
Enucleation	3 30	1	9
Cyclodialysis	4 3	1	3
Strabismus	5 22	2	10
Removal of intraocular foreign body	No postop. pain		1
			Total, 264
			Total eyes operated on, 601

ract extraction with use of procaine HCl and lidocaine HCl, and it was 4 hours 20 minutes with use of Primacaine HCl. It was therefore concluded that anesthesia produced by Primacaine HCl lasted approximately one hour longer than that produced by procaine HCl or lidocaine HCl. Lidocaine HCl had a duration comparable to that of procaine HCl or slightly longer. This was reflected in the number of injections which had to be made through the tubing for the relief of postoperative pain. Some inaccuracy is involved because the observations were subjective, reinjections being made whenever the patient complained of pain sufficient to ask for medication. The error should, however, be comparable for all of the anesthetics. The patients operated on with the use of procaine HCl and lidocaine HCl needed, on the average, two to three injections, while those operated on with use of Primacaine HCl needed only one to two. This difference was not so dramatic as our previous observations with use of U-0045, where the duration of anesthesia was 8 to 10 hours and the vast majority of patients had no significant amount of postoperative pain.

A phenomenon called tachyphylaxis was noted, which has been encountered by others who have employed prolonged local anesthesia, especially in caudal type. This consists of diminishing effectiveness of various local anesthetic agents with repeated injections. We observed this in our continuous retrobulbar anesthetic technique with use of procaine HCl, lidocaine HCl, and Primacaine HCl. Following the first reinjection, subsequent injections frequently were less effective and lasted a shorter time. This could be overcome by using a different anesthetic agent. No noticeable difference in duration of anesthesia was noticed in any of these local anesthetic agents with or without hyaluronidase. It is obvious, however, that our clinical observations could not be as accurate as those in rabbits had been because of the subjective nature of the data.

C. Comparison of the Effect of Pilocarpine on Postoperative Pain.—We attempted to evaluate the effect of pilocarpine upon postoperative pain when it was instilled at the time of cataract extraction and found it to be an important factor (Table 5); 151 patients were operated on without pilocarpine, and 296, with pilocarpine instilled at the time of extraction. There were 89 (59%) of 151 patients with no pilocarpine who complained of postoperative pain, while 232 (78%) of the patients receiving pilocarpine at the time of extraction complained of pain. The time of onset of pain was approximately the same whether or not pilocarpine was used but began approximately one hour later with Primacaine HCl than with procaine HCl or lidocaine HCl. A larger percentage of those patients receiving no pilocarpine were relieved by one injection of anesthetic solution, whereas only a small per cent of those receiving it were relieved by one injection. Many more of this group needed two, three, and even more injections, indicating the severity and

TABLE 5.—*Study of Postoperative Pain in Cataract Extraction*

Anesthetic Agent	Without Pilocarpine at Extraction								With Pilocarpine at Extraction						
	Operated On, No.	Having Pain, No.*	Injections for Relief of Pain, No.						Operated On, No.	Having Pain, No.	Injections for Relief of Pain, No.				
			1	2	3	4	5	6			1	2	3	4	5	6
Procaine HCl 0.8%	51	25 (49)	11 (44)	8 (32)	6 (24)				90	70 (78)	22 (31)	22 (31)	22 (31)	4 (6)		
Lidocaine HCl 0.1%	50	33 (66)	17 (52)	7 (21)	5 (15)	2 (6)	0	2 (6)	53	46 (87)	11 (24)	12 (26)	6 (13)	7 (17)	5 (11)	4 (9)
Primacaine HCl 1.5%	50	31 (62)	26 (84)	5 (16)					153	116 (76)	70 (60)	36 (31)	4 (3)	6 (5)		
Total	151	89 (59)	54 (62)	20 (22)	11 (12)	2 (2)		2 (2)	296	232 (78)	103 (49)	60 (25)	32 (14)	17 (7)	5 (2)	4 (2)

* Percentages given in parentheses.

duration of the pain. In comparing the three anesthetic agents, fewer injections of Primacaine HCl were needed than of procaine HCl or lidocaine HCl. This probably reflected greater duration of action of Primacaine HCl.

D. Subconjunctival Injection.—Procaine HCl, lidocaine HCl, and Primacaine HCl are all effective anesthetic agents when injected subconjunctivally. None caused undue local irritation.

E. Facial Akinesia.—Procaine HCl, lidocaine HCl, and Primacaine HCl were used for facial akinesia by a modified O'Brien technique. The entire area over the neck of the mandible, extending toward the external canthus, was infiltrated with 10 to 20 cc. of anesthetic solution. All of the anesthetic agents produced excellent blocks and seemed innocuous.

F. Minor Surgery.—Operations were done to remove chalazia, verruccae, and other lid tumors, with excellent anesthesia and no ill effects.

Comment

Results of experimental and clinical studies comparing the anesthetic properties of procaine HCl, lidocaine HCl, and Primacaine HCl have been presented. This is part of a study directed toward finding an anesthetic agent of 8 to 10 hours' duration, which would avoid nearly all postoperative pain in ocular surgery. Further experience with a technique for continuous retrobulbar anesthesia previously described by one of us (H. G. S.) has also been presented.

An anesthetic agent, U-0045, which we had previously studied, was an excellent anesthetic agent for retrobulbar use, with a duration of 8 to 10 hours, but, for various reasons, the drug has not been made available commercially. It, however, so clearly demonstrated the value of prolonged anesthesia that a technique for continuous anesthesia by repeated injections through a polyethylene tube retained in the muscle cone was developed. This has proved to be very satisfactory and has permitted us to eliminate the use of such analgesics as codeine, meperidine (Demerol), and morphine, with their occasional complications, and therefore contributes to a smooth postoperative course.

Although pain can be avoided satisfactorily, the method is not ideal. Tubing must be inserted into the muscle cone, and the apparatus must be sutured to the skin in front of the ear. Though we have had no complications, any method which involves a foreign body in the orbit is theoretically objectionable, and contamination of the apparatus must always be considered. A further search for an ideal long-lasting local anesthetic solution therefore should be continued.

The present study shows that Primacaine HCl has a duration of approximately one hour longer than that of procaine HCl or lidocaine HCl. Its greater duration and possibly greater effectiveness are also demonstrated by the need for fewer injections for relief of postoperative pain than when either procaine HCl or lidocaine HCl is employed. It produces excellent anesthesia and is nonirritating, and, in our experience

with more than 300 operations, it was nontoxic. These facts are supported by extensive reports in the dental literature, where the anesthetic is now considered by many to be the anesthetic agent of choice. The ideal anesthetic solution for ophthalmologic surgery should, however, have a considerably longer action.

Summary

Primacaine HCl produces excellent anesthesia for ophthalmic surgery, is nonirritating, and is, in our experience, safe. Because it differs chemically from procaine HCl, its use is said to be permissible in patients who are sensitive to procaine HCl.

Primacaine HCl has a duration of approximately one hour longer than that of procaine HCl or lidocaine HCl.

In further observations, continuous retrobulbar anesthesia with use of a polyethylene tube retained in the muscle cone has proved to be effective in relieving postoperative pain and has been safe in more than 600 patients.

Pilocarpine nitrate, instilled at the time of cataract extraction, causes a significant increase in postoperative pain.

317 S. 17th St. (3).

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The Differential Diagnosis of Tapetoretinal Degenerations

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1. Definition of Tapetoretinal Degenerations

Tapetoretinal degenerations are due to partial or complete destruction of a normally developed retina, not as a result of exogenous inflammatory or traumatic influences but due to endogenous influences which cause premature degeneration of the tissue. This retinal "abiotrophy" is hereditary; it is not known whether the action of the pathological gene is of the humoral, neural, or toxic type or whether the condition is simply based on diminution of the viability of retinal cells.

Idiopathic retinitis pigmentosa is the prototype of a tapetoretinal degeneration. Various authors have grouped round this extremely characteristic affection a variable number of other affections of the ocular fundus, more or less characteristic and more or less closely related to retinitis pigmentosa, which are all referred to as tapetoretinal degenerations.

Retinitis punctata albescens, for instance, is nearly identical with retinitis pigmentosa, whereas senile macular degeneration is only remotely connected with it, especially as regards its general symptoms. Essential hemeralopia is considered a tapetoretinal degeneration by certain investigators—a conception which will be demonstrated to be erroneous.

It would seem to me that, if regrettable confusion is to be avoided, it is absolutely necessary to safeguard the conception "hereditary abiotrophy" in the definition of tapetoretinal degenerations. This principle will enable us not only to define with exactness such diseases as are included in this group but also to distinguish such affections as should be differentiated from tapetoretinal degeneration, i. e., functional retinal anomalies, congenital forms of chorioretinitis, and acquired chorioretinitis.

Functional anomalies of the retina can be defined as follows: They are strictly hereditary affections (with no or hardly any variability in phenotypical expression), which are strictly congenital and stationary and strictly localized to the eye; the functional changes are extremely specific, moreover, as they are determined by selective dysfunction of one or several components of the mechanism of vision, which are disturbed in the whole retina. The fundus of the eye is ophthalmoscopically normal or shows only minimal nonprogressive lesions.

Congenital forms of chorioretinitis show changes in the ocular fundus produced by exogenous pathological factors (infectious, toxic, or metabolic) before the subject affected is born. They are not, therefore, due to the action of a pathological gene, but pseudoheredity is sometimes seen. Evidently, certain acquired forms of chorioretinitis of early childhood cannot be distinguished, afterward, from congenital forms.

It could hardly be considered necessary to give a definition of acquired forms of chorioretinitis.

Table 1 summarizes these definitions and the essential elements in the differential diagnosis between the four groups of affections of the ocular fundus.

From the Ophthalmological Clinic of the University of Ghent, with the collaboration of Dr. Guy Verriest.

Guest speaker's address read before the Section on Ophthalmology of the American Medical Association, New York, June 5, 1957.

TABLE 1.—*Differential Diagnosis Between the Tapetoretinal Degenerations and Other Groups of Chorioretinal Diseases*

	Heredity (Variability in Phenotypic Expression)	Somatic Lesions	Ophthalmoscopic Picture	Functional Lesions	ERG (Weak Stimuli)	Beginning	Evolution
Tapetoretinal degenerations	Yes (very frequent)	Very frequent; typical neurol. & diencephalo-hypophyseal disorders	Pathological; degenerative, bilateral, & symmetric	Localized area at first; all functions touched (→ blindness or absolute scotoma)	Normal, subnormal, or absent	Generally late	Generally progressive
Functional abnormalities	Yes (very rare)	No	Normal or nearly normal	Same lesion in whole retina; some functions exclusively disturbed	Normal or selective loss of b_1 or b_2	Present at birth	Absolutely stationary
Congenital chorioretinitis	No	Very frequent; typical visceral & neurological disorders	Pathological; generally bilateral & symmetric	None or as tap-ret. deg.	Generally normal or subnormal	Present at birth	Generally stationary
Acquired chorioretinitis	No	Possibly acquired inflammatory disorders	Pathological; often not bilateral or not symmetric	As tap-ret. deg.	Generally normal or subnormal	Late	Progressive & later stationary

Having thus outlined our subject in general, we can now enter into detail. Diagnostic methods are to be discussed first, followed by an analysis of the characteristic symptoms of the various diseases. To end with, different elements of differential diagnosis will be applied to certain specific complicated cases.

2. Diagnostic Methods

Five different groups of diagnostic methods can be distinguished: genetic investigation, general examination, objective ocular examination, functional ocular examination, and investigation of development.

1. *Genetic Investigation.*—The genetic investigation in any particular case naturally starts with an interrogation of the patient as to his family. This interrogation should be extremely detailed, comprising two stages. A. In the first place, the completest possible history is taken as to the genealogy of ascendants, descendants, and collaterals, with special reference to possible consanguinity, miscarriages, deaths in early childhood, and twin births. B. Information is then obtained as to the general and ocular condition of each sibling. Age and cause of death are recorded, and all congenital malformations are painstakingly investigated. As to ocular lesions, emphasis should be placed on characteristic symptoms (hemeralopia, color blindness, nystagmus, bearing, age of onset and development) rather than on "bad vision" and the wearing of spectacles, which are of less interest.

This first interrogation is the basis of the familial examination; the genealogical tree should be verified and completed on each occasion. Presumably normal subjects are examined with as much care as presumably affected subjects. Only in this manner is it possible to detect gene carriers and abortive forms as well as interesting correlations.

A patient's affection can be regarded as hereditary (*a*) if there are other similar cases in the family; (*b*) if there are heterozygotic stigmata in certain subjects, if an autosomal or sex-linked recessivity or irregular dominance can be presumed; (*c*) if there is consanguinity among the ascendants, if an autosomal recessivity can be presumed; (*d*) if the diagnosis of an affection reputedly strictly hereditary is established. This is the case, even if there are no other instances in the family, if there is dominance, in which case a recent mutation is probably involved.

On the other hand, the affection is probably not hereditary if it occurs in only one of a pair of monozygotic twins. If the affection is seen in both it may in excep-

tional cases be due to a factor acquired during intrauterine life.

The genetic diagnosis is important not only as an aid in establishing the diagnosis of the affection but also as an aid in establishing prognosis.

2. *General Examination.*—General examination is of paramount importance in the diagnosis of tapetoretinal degenerations. The clinical examination as done routinely is chiefly designed to detect acquired lesions and should be supplemented by a search for congenital anomalies and a study of the neuropituitary condition. For this purpose a neurological examination is made, with an EEG. It will be shown that the EEG is an important factor in differential diagnosis.

3. *Objective Ocular Examination.*—Examination of the anterior segment should not be neglected. The detection of sequelae of an old uveitis suggests an inflammatory affection of the ocular fundus, but it should be borne in mind that the Fuchs type of iridic heterochromia may constitute a symptom of peripheral tapetoretinal degeneration. On the other hand, if a posterior polar cataract is an argument in favor of a degenerative process, yet certain changes in the anterior segment (e. g., reduction of the corneal diameter and nuclear cataract) are indicative of an exogenous intrauterine affection.

Examination of the ocular fundus is evidently concerned with the investigation of signs more or less characteristic of each group of affections, viz., waxy atrophy of the optic disc, thickness of retinal vessels, grayish varnished aspect, white-yellowish points, and star-shaped pigmentations are characteristic of peripheral tapetoretinal degenerations, and macular "snail slime" changes and yellowish or reddish punctates, of juvenile macular degenerations. An aspect of macular degeneration or simply absence of foveal reflection is seen in typical achromatopsia. Diffuse gray or yellow-gold coloration is seen in Oguchi's disease. There is a total lack of ophthalmoscopic lesions in the other functional anomalies. Congenital chorioretinitis often shows a pepper-and-salt aspect. Acquired chorioretinitis shows zones of total retinal and choroid destruction and gross pigmented or atrophic plaques.

The distribution of lesions, in particular, should be verified; in the case of tapetoretinal degeneration these are as a rule perfectly symmetrical in the two eyes. The bilaterality of the affection is an important factor in the diagnosis.

4. *Functional Ocular Examination.*—Ocular motility should always be determined. Nystagmus should be determined whether this is due to neurological influences (jerking nystagmus) or to amblyopia with or without macular aplasia (undulatory nystagmus); electronystagmography (ENG) can be used for this purpose.

Examination of the sensory function naturally yields the most interesting data.

Central visual acuity can be determined not only under normal photopic conditions but also as a function of luminance. In the case of beginning macular lesions the mesopic visual acuity (the curve representing the acuity-luminance ratio) is considerably more markedly affected than the central photopic acuity.

Examination of the photopic field of vision should be painstakingly thorough. I use the Goldmann perimeter, which offers great advantages as to upkeep, registration of results, and possibilities (spatial summations).

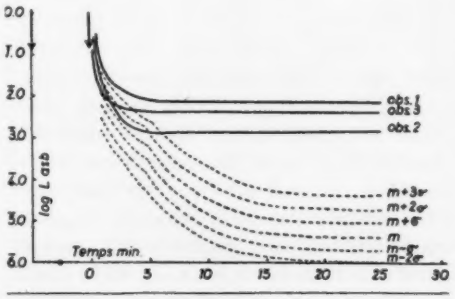


Figure 1

As to dark adaptation, I prefer the use of "integral" thresholds, pertaining to the entire field of vision, to the use of thresholds corresponding with a determined retinal area. In this manner I obtain a curve more perfectly representative of the overall affection of the retina. For this purpose I have used the Goldmann-Weekers adaptometer (second model). Figure 1 shows the distribution of normal curves obtained by my technique (preadaptation: 2000 footcandles during five minutes on the entire visual field).

The importance of examination of the scotopic field of vision has previously been demonstrated by Miss Sloan. For a study of the distribution of absolute thresholds in complete darkness I first used the Livingston tests, which revealed that the central scotoma in darkness often shows marked and very early changes (Fig. 2 shows normal central scotomata in darkness, determined by this technique). At present I am using a new test presenter, which was designed according to my specifications (Fig. 3).

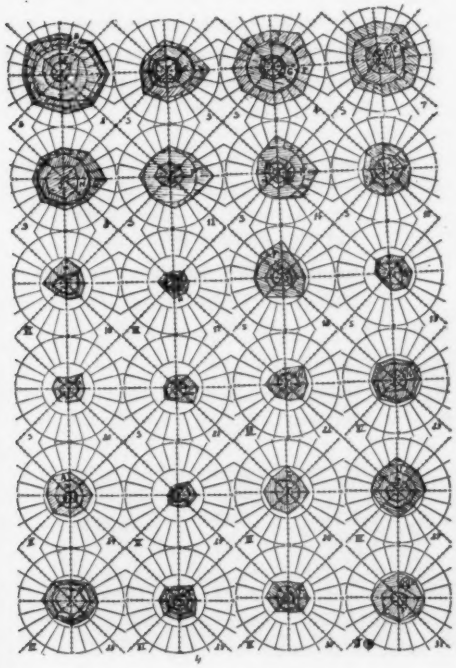


Figure 2

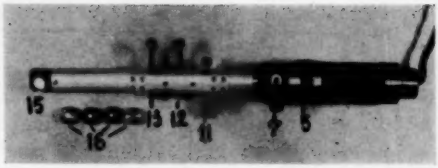


Figure 3

I have long been convinced that examination of central color sense is of extremely great diagnostic value, as was demonstrated by the almost forgotten investigations of König and Köllner. In the study of acquired dyschromatopsia I use the old colorimetric apparatus, viz., Helmholtz color mixing apparatus, and the Nagel anomaloscope, by which it is possible not only to establish with certainty all congenital anomalies in color vision but also to study acquired forms of color blindness. The clinical diagnosis can be made on the basis of the Panel D-15 and the 100-hue test of Farnsworth, which rapidly produce extremely significant results in dyschromatopsia, whether acquired or congenital.

Besides these subjective sensory function tests, I have used objective sensory tests. The first factor studied in this respect was the electrical resting potential of the eye. This can be estimated by electro-oculography if all factors involved are standardized. The amplitude of deflections following ocular movements is representative of the resting potential of the eye. This potential is influenced by the condition of retinal adaptation. Figure 4, pertaining to normal eyes, shows the fall in electro-oculographic values during dark adaptation. I have demonstrated that, in the case of pathological affections of the ocular fundus, the amplitude of this fall is correlated with the amplitude of the b wave in the scotopic ERG.

I then studied the retinal action potential induced by light stimulation: the electroretinogram (ERG). First I used the Karpe apparatus (white light stimulation, 80 lux for 0.04 second, registration with the aid

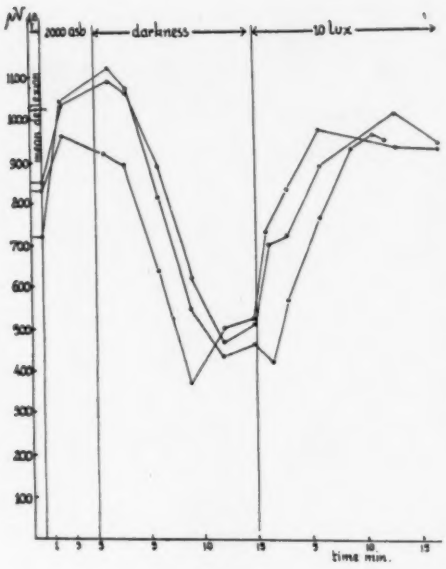


Figure 4

of a modified ECG with an over-all time constant of 1.5 seconds, $m \pm 2\sigma$ of the scotopic b wave, 250μv. to 500μv.), and then, a neon light source, which permits the dissociation of the photopic b_1 wave and the scotopic b_2 wave (registration with the aid of an EEG with an over-all time constant of 0.20 second, $m \pm 2\sigma$ of the scotopic b wave, 150μv. to 300μv.), in conjunction with a xenon light source, which permits attaining extremely intensive stimulations and of studying the a wave in particular (energy values of stimulations: 0.1, 0.2, and 0.6 joule; technique of registration as that used with neon light). Figure 5 shows examples of normal responses obtained by these three different techniques.

The examination is completed by a study of the occipital reactions to light stimulation, ensuring that only one eye at a time is stimulated. In the majority of cases a specific occipital reaction can be produced by means of a strong stimulus (at least in normal subjects); this reaction consists of a series of alternately positive and negative oscillations: the b, c, and d waves (Fig. 6). The retinocortical time is obtained by subtraction of the latent time of the ERG b wave from the latent time of the occipital b wave (Laue and Monnier).

A combination of all these function tests makes it possible to determine what might be called the functional syndrome in any particular case. This functional syndrome associated with chorioretinal affections differs from case to case.

5. *Investigation of Development.*—Development is investigated partly by means of the history and partly by regular follow-ups of morphological and functional symptoms. It is not only of diagnostic value (tapetoretinal degeneration as a rule shows slow aggravation, which is continuous and identical with that seen in the outer affected members of the same family) but is also an important prognostic sign.

3. Analysis of the Symptoms of Tapetoretinal Degeneration and of Certain Other Groups of Affections of the Ocular Fundus

A. Tapetoretinal Degenerations (Table 2)

(*A*) *Peripheral Tapetoretinal Degenerations.*—1. Retinitis Pigmentosa: (*a*) Generalized retinitis pigmentosa. (1) Heredity. Retinitis pigmentosa is as a rule transmitted by the autosomal recessive route, and in a

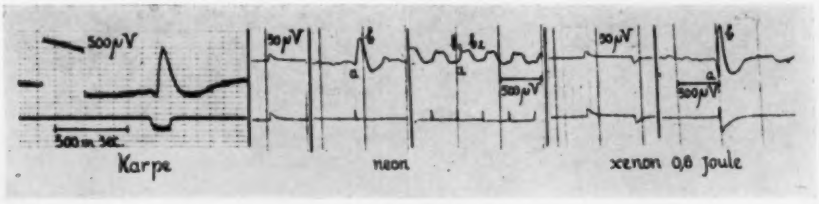


Figure 5

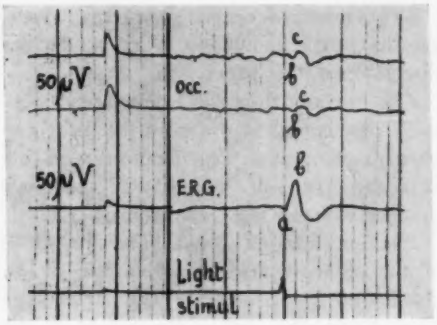


Figure 6

few exceptional cases, also by dominant or sex-linked recessivity.

In pigmentary degeneration with a continuous heredity the general symptoms (deaf-muteness, affections of the central nervous system, idiocy) are considerably less common than in pigmentary degeneration with a discontinuous heredity, and the ocular affection itself has a relatively milder course.

Falls and Cotterman's sex-linked pigmentary retinopathy is characterized, in men, by typical retinitis pigmentosa with progressive choroid sclerosis, leading to complete blindness. The heterozygotic or conducting female shows a "tapetal reflex," i. e., a brilliant, scintillating, golden reflection spread over the entire retinal surface but most pronounced at the level of the macular and the perimacular region, whence it progressively diminishes toward the periphery. This reflection, which is probably due to an irregularity in the thickness of the vitreous membrane, is not associated with any deficiency of vision.

(2) General symptoms. Pigmentary degeneration of the retina is often associated with other anomalies, which constitute the "neuro-ocular or cerebroretinal syndromes"; these anomalies result from the same heredodegenerative primitive process and constitute the expressions of one and the same abiotrophic gene. The following conditions may thus be found to coexist: (*a*) deaf-muteness due to atrophy of the organ of Corti and to degeneration of the acoustic nerve; it is found in 10% of cases at least; (*b*) mental deficiency to the point of idiocy, which is seen in 4% of cases; (*c*) Bardet-Biedl syndrome, characterized by four chief symptoms, viz., pigmentary degeneration of

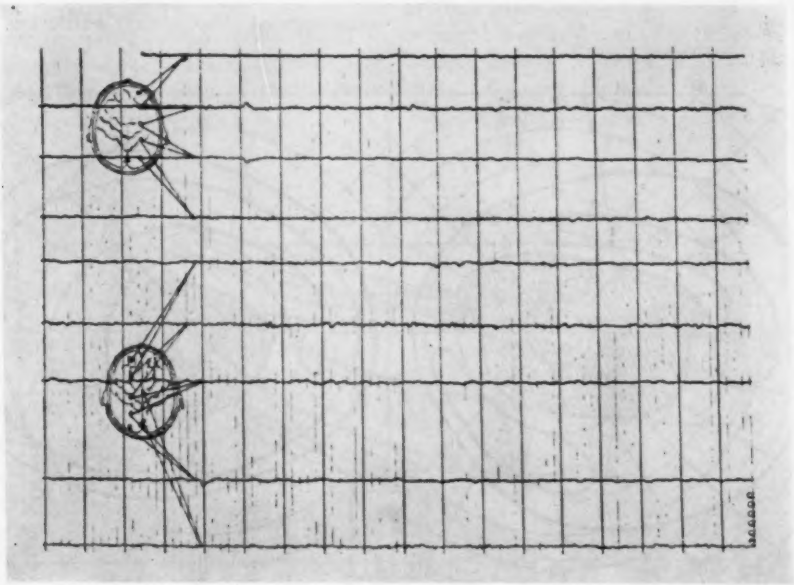


Figure 7

the retina, adiposogenital dystrophy, polydactylism, and mental deficiency; (*d*) hereditary spinopontocerebellar ataxia (Friedreich's spinal type, Pierre-Marie's cerebellar type, Charcot-Marie's neural amyotrophy, spasmodic paraplegia); (*e*) amaurotic idiocy.

(3) EEG changes. These are frequently seen in retinitis pigmentosa; more than 80% of patients show diffuse dysrhythmia and polymorphism of low voltage, indicating generalized encephalic disturbances (Fig. 7). On the basis of bioelectrical data obtained in 19 cases, four groups can be distinguished: (*a*) diffuse dysrhythmia and polymorphism of remarkably low microvoltage in 10 cases; (*b*) diffuse polymorphous dysrhythmia of low voltage, predominant in one or several derivations in 3 cases; (*c*) diffuse polymorphous dysrhythmia of moderate to high microvoltage in 4 cases, including 3 presenting, among other changes, paroxysmal bilateral hypersynchronous dysrhythmia; (*d*) normal records were seen in 2 cases.

The EEG changes are therefore of very great importance in the differential diagnosis in cases offering difficulties of interpretation.

(4) Objective ocular symptoms. These are too well known to warrant detailed discussion in this paper.

(5) Functional ocular examination. Retinitis pigmentosa is not only the most frequent tapetoretinal degeneration seen but also the type in which the functional changes are the most characteristic.

Photopic field of vision. The alterations of the photopic field of vision can be divided into three stages. The first stage (Fig. 8) begins with a depression in the median part of the field (between 20 and 40 degrees); nodes of opacification in this depression give rise to scotoma (annular type). This is initially incomplete but progresses very rapidly and continuously toward the periphery, in which it soon settles, and more slowly to the point of fixation. Sometimes there is a multiple annular scotoma. The central slope is very steep.

In the second stage (Fig. 9) the field of vision is reduced to two zones of perception, viz., a central islet of 15 degrees at a few degrees of radius and with extremely steep slopes and an islet localized at the end of the horizontal temporal meridian. This temporal islet has the form of an elongated strip, always bordering on the

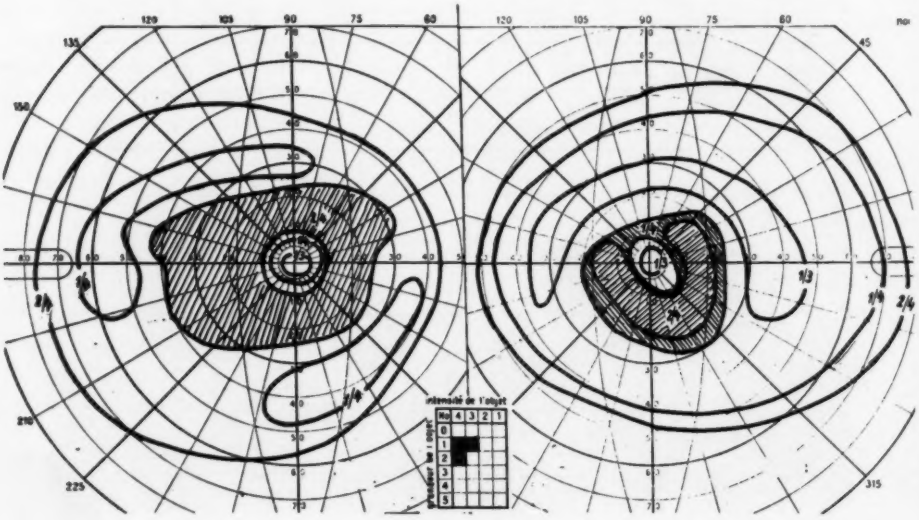


Figure 8

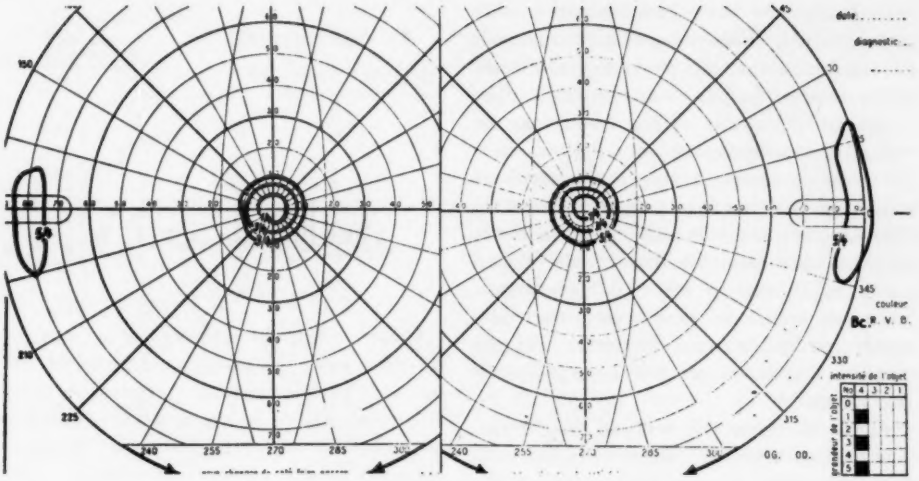


Figure 9

horizontal meridian above and below; its peripheral limits are normal; its central limits show a slight slope and are curved, giving the islet a crescent shape.

The third stage shows the disappearance of one of the two islets, usually the temporal one.

If the pigmentary retinopathy is complicated by a macular affection, there is as a rule a central scotoma, independent of or confluent with the annular scotoma. The morphology can be difficult to recognize in the case of excentric fixation.

Concentric contraction proper, i. e., a generalized depression of the field of vision manifested particularly in the peripheral isopters, constitutes no symptom of retinitis pigmentosa.

Curve of global dark adaptation. The curve of global dark adaptation shows marked individual variations (Fig. 10). It is sometimes completely normal as to the terminal threshold and as to the curve itself. Nearly always, however, it is pathological. It is frequently biphasic. If the curve of the cones and the α-point are not displaced

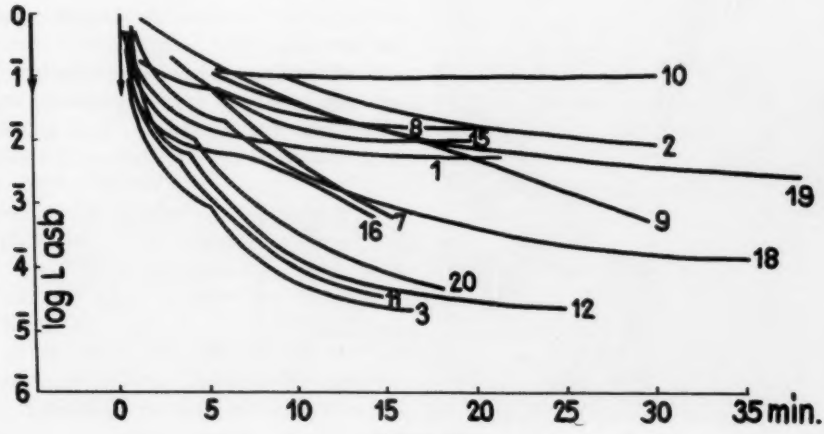


Figure 10

considerably in time as compared with normal cases, then the curve of the rods is retarded so that the physiological threshold is reached late or even not at all. The height of the curve of the cones may be normal or pathological. In the majority of cases in advanced stages the curve of adaptation is monophasic; there is no photochromatic interval. In such cases the curve may be identical with that of the foveal cones, as is seen in essential hemeralopia. Later, the curve is considerably more elevated, and the terminal thresholds indicate that the thresholds of cone perception are also affected.

Field of vision in reduced brightness. The field of vision in reduced brightness is characterized by marked aggravation of the deficiencies observed at the photopic perimetry.

Scotopic field of vision. The scotopic field of vision is of great importance, as its changes are seen earlier than those in the curve of global adaptation. In the annular scotoma stage the thresholds are increased at the level of the latter, whereas they may be normal at the level of the temporal periphery and in the center of the field, where the physiological central scotoma in darkness may be seen. Later, the maximal sensitivity corresponds with the fovea.

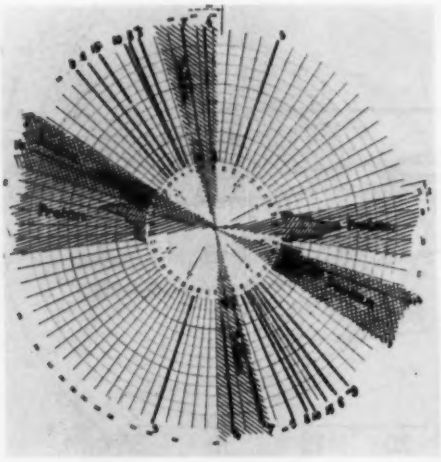


Figure 11

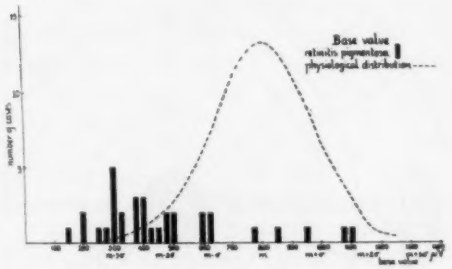


Figure 12

Color vision. In retinitis pigmentosa, as in other tapetoretinal degenerations of the so-called peripheral type (retinitis punctata albescens, Fuch's atrophia gyrata, generalized choroid sclerosis), there is dyschromatopsia which affects predominantly the blue-yellow discrimination. The neutral axis is extremely variable in direction from case to case, ranging from that of hypothetic congenital tetartanopia to that of congenital deuteranopia. It is as a rule found between that of deuteranopia and that of tritanopia, and most frequently in the proximity of the latter (Fig. 11). The Nagel anomaloscope nearly always showed a protanomalous quotient.

Electro-oculography. A normal base value was found in only 13 out of 33 eyes affected by retinitis pigmentosa; in 15 the value was below 2σ below the mean, and in 5 it was below 3σ below the mean (Fig. 12). The decrease in value normally seen during dark adaptation was nearly always lacking (Fig. 13).

Electroretinography. The complete lack of ERG response from the earliest stages of retinitis pigmentosa on is at present a well-established notion. It should be pointed out, however, that very intensive light stimulation nonetheless produces a response in the form of a characteristic isolate a-peak (Fig. 14).

Cortical reactions to light stimulation. As a rule there is no specific occipital response; if it exists, however, it is deformed and retarded. In the majority of cases there is not even an α-blocking; if it exists it is always hardly demonstrable.

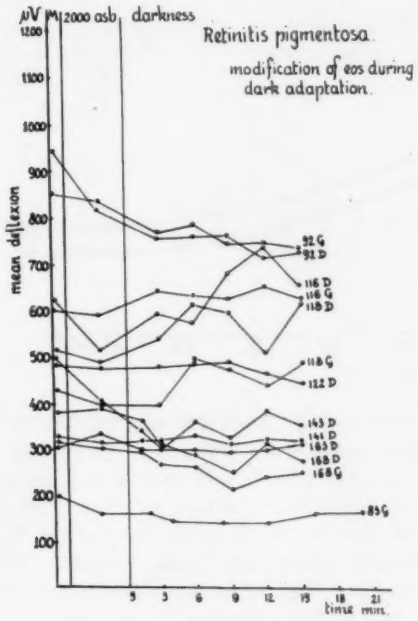


Figure 13

The EEG record is not or is hardly changed in the course of intermittent light stimulation.

(*b*) Localized retinitis pigmentosa. In exceptional cases the degenerative process can be localized to one eye or to a certain part of the ocular fundus. This localized retinitis pigmentosa may occur in three types: (*a'*) unilateral retinitis pigmentosa, of which only some 20 cases are on record as definitely not acquired and definitely not bilateral with retarded progress in one eye. The functional changes in the affected eye are identical with those seen in typical bilateral cases; (*b'*) retinitis pigmentosa in sectors is extremely rare; the changes in the ocular fundus are always strictly symmetrical; (*c'*) central or pericentral retinitis pigmentosa is more frequently seen; some 30 cases have so far been reported.

Retinitis pigmentosa localized to a certain part of the ocular fundus is obviously extremely interesting from a functional point of view. The photopic field of vision shows deficiencies corresponding with the lesions in the ocular fundus. The global light sense is considered almost normal in the rare cases of degeneration in sectors. It is, on the other hand, often pathological in the central forms. Adaptation in our cases was extremely slow, but the final threshold was normal in one of our patients (Fig. 15). The scotopic field of vision shows that the lesions are in fact more extensive than is indicated by the photopic field of vision. The affected zones are obviously extremely hemeralopic. The ERG was manifestly subnormal or even absent in the majority of our cases. In any case, however, it is an important prognostic sign, as will be shown in the fourth section of the paper.

2. Retinitis Punctata Albescens: According to Fuch's original monograph the affection is characterized by seven essential symptoms, viz., hemeralopia, low central visual acuity, narrowing of the field of vision, characteristic ophthalmoscopic features, consanguinity of ascendents, familial occurrence, and onset in early childhood.

In view of the work of Lauber, two clinical entities are as a rule distinguished: "fundus albipunctatus cum hemeralopia," characterized by stationary or benign development, a normal field of vision (or

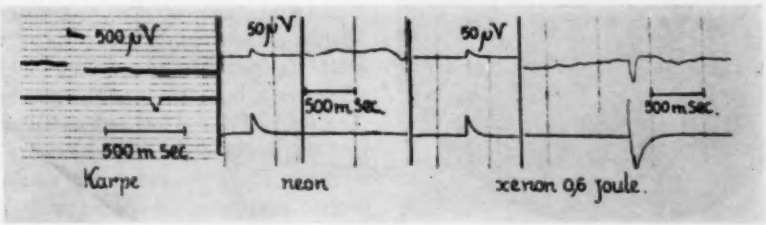


Figure 14

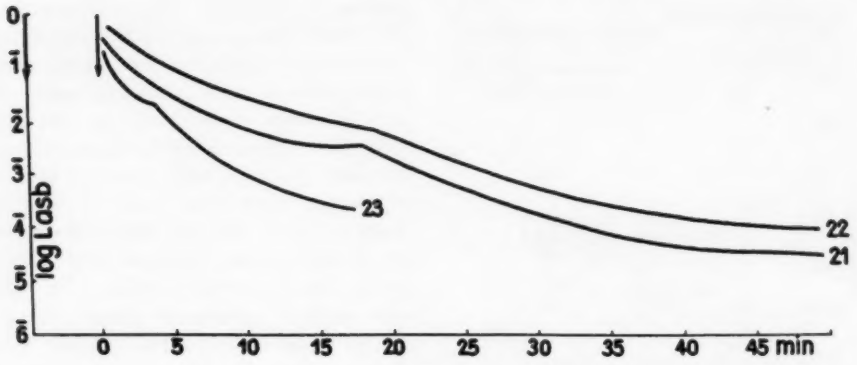


Figure 15

slightly narrowed), and a more or less characteristic appearance of the ocular fundus (Fig. 16), and, on the other hand, true "retinitis punctata albescens," which is progressive and associated with narrowing of the field of vision down to the point of tubular vision, changes in color sense, a marked change in central visual acuity, and an ocular fundus in which pigments are mixed with white spots. The prognostic significance of this distinction has recently been emphasized again by Franceschetti and Chomé-Bercioux.

Other investigators have gone much farther in confirming that the albipunctatus fundus is nothing but a variety of essential hemeralopia, even being identical with Oguchi's disease (Giannini).

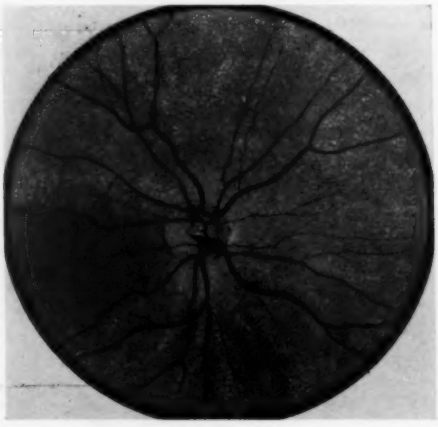


Figure 16

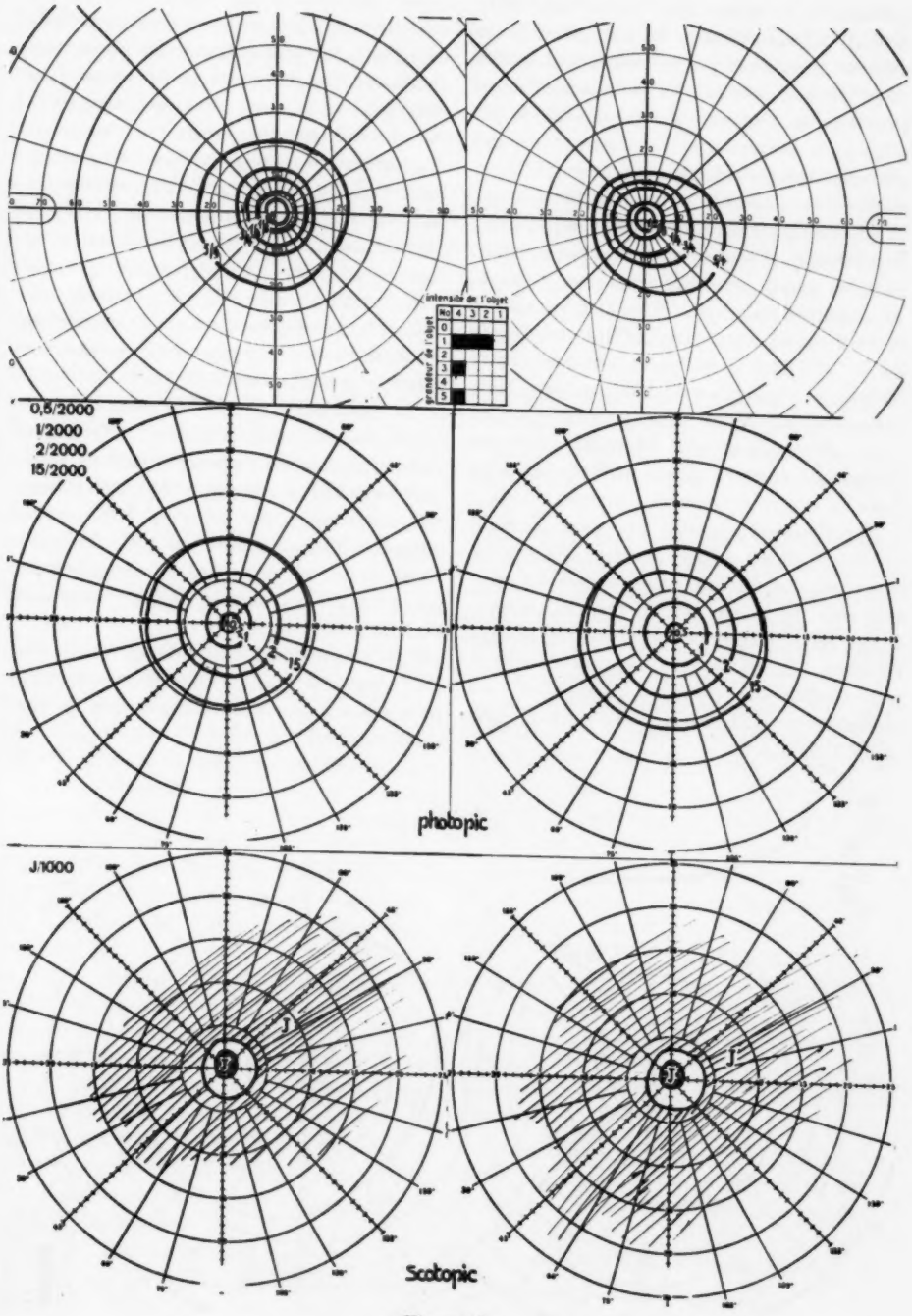
It is beyond doubt that this affection may show considerable differences in its course from case to case and that it may remain stationary in certain patients. Yet I believe that there is no reason to believe that two distinct types really exist; Lauber, too, maintains that all transitional forms are to be found between the two extreme types of development.

Visual function tests fail to reveal any relationship with essential hemeralopia in general and with Oguchi's disease in particular.

The heredity is as a rule of the autosomal recessive type.

The general symptoms of retinitis punctata albescens are completely identical with those of retinitis pigmentosa (EEG changes, association with the Bardet-Biedl syndrome, etc.).

The functional changes are often different, however, the photopic field of vision as a rule showing true concentric narrowing, without annular scotoma (Fig. 17). This occurs only if the affection is associated with pigmentations. The curve of adaptation shows changes similar to those seen in retinitis pigmentosa (Fig. 1); there may be considerable slowing down. The field of vision on reduced illumination and the scotopic field of vision are characteristic: There is extremely marked concentric narrowing compared with photopic findings. In our three cases the ERG was


intensité de l'objet
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grandeur de l'objet
0,5/2000
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photopic
1/1000
Scotopic

Figure 17

different: In one case (associated with retinal pigmentations) it was absent; in another it was very subnormal, and in the third it was normal. The last-mentioned case was an example of "fundus albipunctatus cum hemeralopia." Franceschetti and Dieterle also observed a normal ERG, in another case of this particular form.

3. Peripheral Chorioretinal Abiotrophies: I purposely discuss, in the same section, atrophia gyrata, chorioderemia, and generalized choroid sclerosis. The last-mentioned two affections are often difficult to distinguish, and the identity of the two first-mentioned conditions has often been suggested.

(*a*) Atrophia gyrata. Heredity is of the autosomal recessive type. In 90% of cases there is severe concomitant myopia.

Functional symptoms. The photopic field of vision shows either annular scotoma or concentric narrowing which shows no relation with the topography of choroid changes (Fig. 18). Hemeralopia is nearly always reported. In those rare cases in which it was studied the curve of adaptation was monophasic. ERG's have been normal, subnormal, or absent.

(*b*) Choroideremia. Choroideremia is an excellent example of intermediate sex-linked heredity. In males it causes, from early childhood, progressive loss of visual function and increasingly complete atrophy of the choroid and the retina; in the heterozygotic female there is no functional change but merely stationary anomalies of the ocular fundus, characterized by irregular pigmentation, in more or less clearly circumscribed areas; by depigmented retinal zones, and sometimes by peripapillary atrophy. The combination of zones of pigmentation and zones of depigmentation resembles either atypical retinitis pigmentosa or the pepper-and-salt type of chorioretinitis.

In males there is a marked affection of visual function; the photopic field of vision may show either annular scotoma or concentric narrowing; the latter is very marked on reduced illumination. In such few cases as were studied in regard to adaptation the curve was extremely high, remaining biphasic.

(*c*) Generalized choroid sclerosis. The field of vision shows a concentric narrowing or a central scotoma. Hemeralopia is generally seen.

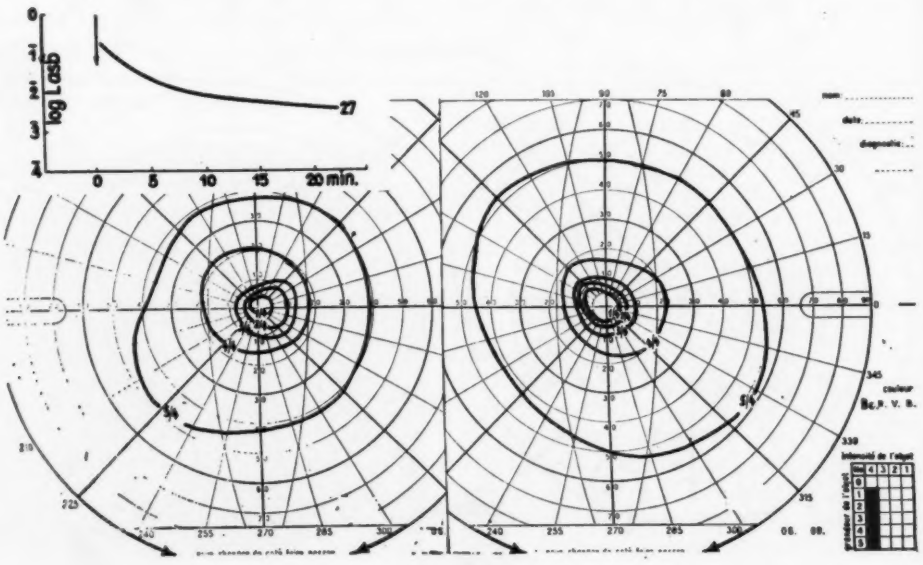

Figure 18

(*B*) *Central Tapetoretinal Degenerations.* This group includes not only the hereditary macular degenerations of the Stargardt type, the central or peripapillary abiotrophic chorioretinal scleroses, and Sorby's pseudoinflammatory dystrophy but also the angioid streaks and senile macular degeneration; the last two affections are also hereditary, and their histological lesions are almost identical with those seen in Sorsby dystrophy.

1. Hereditary Macular Degeneration (Stargardt): A survey of the literature on heredodegenerative affections of the macula shows that the lesions in these cases are evidently polymorphous. Yet there is a marked impression that attempts at introducing different denominations and characteristics have been unjustified, as, separating the so-called typical forms, there are intermediary forms. In fact, all macular dystrophies show essentially the same heredodegenerative lesion. In different families this gives rise to different ophthalmoscopic changes. Its transmission may be dominant or recessive; its onset may be early or late; its course, too, is extremely variable, severe or mild according to the family involved and the age of occurrence.

In all treatises, nevertheless, separate descriptions are given of Best's congenital or infantile form, of which only a few instances are known and of which the heredity seems rather irregularly dominant; the juvenile form of Stargardt, which is the form by far most frequently seen and which is usually transmitted by recessive heredity and in a few cases by the dominant route; the virile form of Behr, which appears after puberty, as a rule toward the age of 20; the presenile form of Behr, which is rather rare and starts between 40 and 60 years of age, and the senile form, to which I have recently drawn attention. In reality, macular heredodegeneration may occur at any age, although it most frequently occurs between 8 and 20 years of age.

The condition affects the two eyes simultaneously and shows a parallel development, slowly but regularly progressive.

Although in exceptional cases there may be stabilization of lesions (Behr), they usually aggravate to give rise, after several years, to complete destruction of the macular region and complete loss of central vision.

The lesion may remain localized to the macula, where it forms a well circumscribed focus of ½ to 1 p. d. (papilla diameter). In as many cases, however, it spreads to cover the entire macular region and to form a central degenerative zone, the limits of which are uncertain, extending over a variable distance of 4 to 5 p. d.

In many cases only the macular region is affected, the remainder of the ocular fundus remaining normal. The retinal vessels are unchanged. Atrophy of the optic nerve is rare.

In many cases a diminution in central vision precedes the first ophthalmoscopic changes by some considerable period of time. In some cases, however, macular alteration may be observed before visual acuity is affected.

(*a*) Ophthalmoscopic features. The ophthalmoscopic features are extremely polymorphous, varying, so to speak, from one family to another. In general, however, the features are identical in the two eyes and in the members of the same family.

The lesion often begins with an irregularity of pigmentation in the macular region, with disappearance of the foveal reflection. This is followed by the appearance of grayish-yellow spots, at first hardly noticeable but subsequently more marked and assuming an orange hue. Between these spots a dotting of black pigment is seen, accumulating to form small piles of irregular shape.

The yellow spots multiply, enlarge, become pigmented at the margins, and sometimes invade the entire central zone. They may become confluent to form a sharply circumscribed ellipsoid focus, more or less extensive, of grayish-yellow color. This focus, which becomes increasingly pigmented through the years, finally atrophies

and becomes transparent, showing some choroid vessels.

Numerous other ophthalmoscopic features have been described, but in general it can be said that the lesion is either of the atrophic or of the pigmentary type.

The group of hereditary macular degenerations also includes Tay's choroiditis and Doyne's choroiditis, which differ from the condition described by Stargardt only as to their morphology.

(*b*) General symptoms. As compared with retinitis pigmentosa, hereditary macular degenerations are more often accompanied by amaurotic idiocy than by symptoms of the Bardet-Biedl syndrome.

(1) Macular degeneration with dementia. The earlier macular degeneration occurs the more severe it is and the more frequently it is associated with mental symptoms. These tend to develop towards dementia, paralysis, and death; as a rule, they are not seen if the lesions occur after puberty.

Some investigators do not presume any connection between cerebromacular degeneration of the Tay-Sachs or the Vogt-Spielmeyer type and the Stargardt disease, as in families with macular degeneration no progressive neural lesions are observed and as in families affected by amaurotic idiocy no isolated cases of macular dystrophy are observed. It may nevertheless be pointed out that the Tay-Sachs (infantile) form shows generalized degeneration of the ganglion cells of the central nervous system; no generalization is seen any longer in the form known as juvenile, and in certain tissues, e. g., those of the medulla and the cerebellum, they may remain intact. It is an established fact, furthermore, that the slower the heredodegenerative process the slower, more benign, and more localized its development. The majority of macular degenerations only occur after the age of 8, whereas the majority of cases of amaurotic idiocy occur before that age.

(2) Macular degeneration with Bardet-Biedl syndrome. There is, as a rule, dotted macular degeneration associated with atrophy and fine pigmentation of the peripheral part of the retina.

(3) Electroencephalograms. In the Stargardt type of macular degeneration the EEG may show changes similar to those seen in retinitis pigmentosa (dysrhythmia, microvoltage).

(*c*) Functional symptoms. The photopic field of vision is characterized by the presence of an absolute or relative central scotoma. In cases showing peripheral retinal changes there is sometimes an affection of the corresponding parts of the field of vision. In the case of isolated macular lesions the peripheral field of vision was invariably normal.

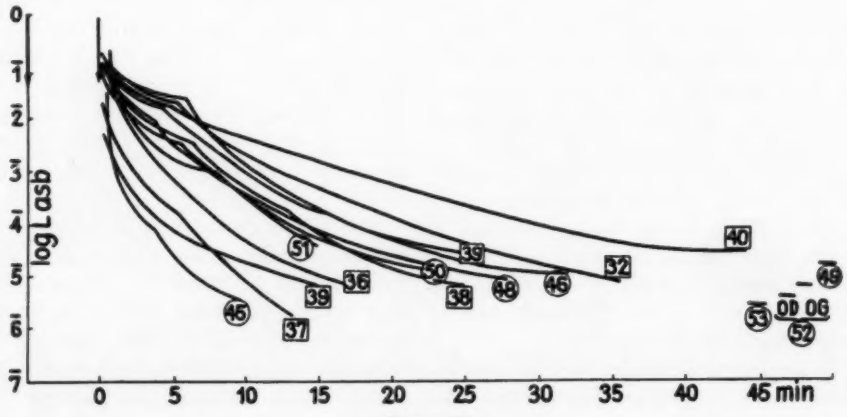

Figure 19

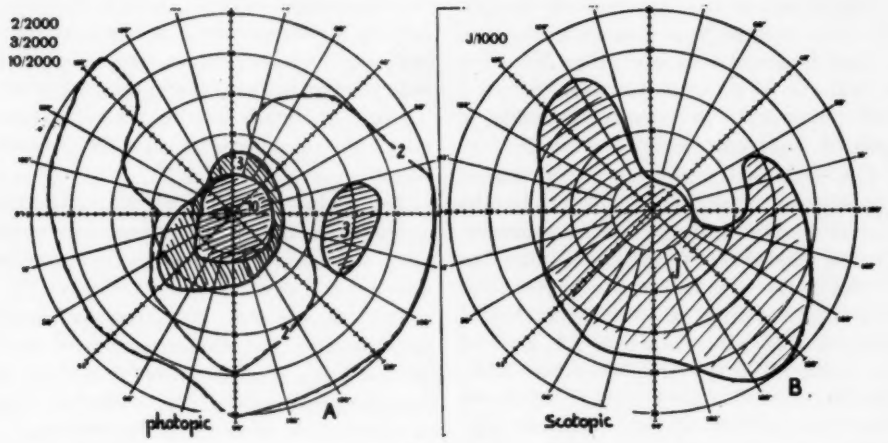

Figure 20

In the case of peripheral lesions the curve of adaptation is often markedly changed; if the lesions are exclusively central, the curve is either normal or subnormal (Fig. 19).

The scotopic field of vision is of great interest in cases showing a paucity of symptoms or asymptomatic cases. Macular hemeralopia is often demonstrable; in some cases it is perhaps due to amplification of the gradients in scotopic vision; in other cases, however, there is clearly a specific affection of night vision (Fig. 20). Campimetric findings in light can be normal; those obtained in darkness may also be normal (cases of macular heredodegeneration in which there are no functional disorders).

There is as a rule dyschromatopsia, affecting chiefly the red-green vision.

Electro-oculogram. The base value is usually normal, as is its decrease during dark adaptation, except in cases in which the ERG is negative.

The ERG is as a rule subnormal or negative in cases showing functional defects

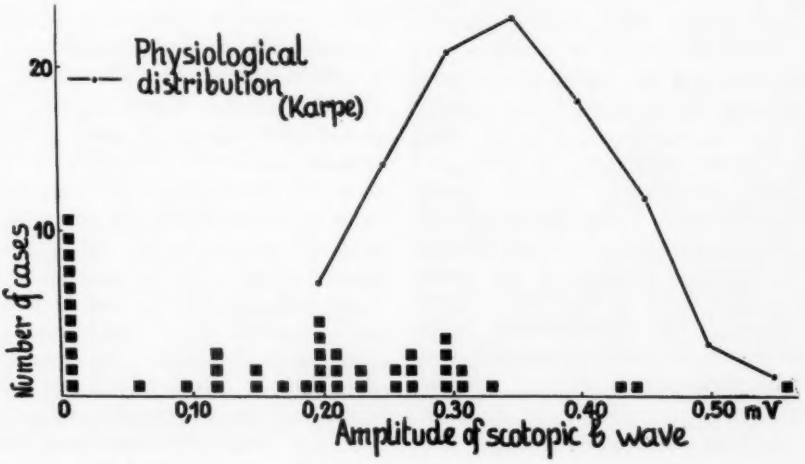

Figure 21

of importance or marked peripheral changes. Yet even in these cases it is not exceptional to find a normal response (Fig. 21). The b_1 wave is in no case selectively affected. The response is of normal amplitude in cases of amaurotic idiocy.

2. Central and Peripapillary Abiotrophic Chorioretinal Sclerosis: The fact that choroid sclerosis and tapetoretinal degeneration are related is shown by the connection of the former with retinitis pigmentosa. This is in fact often associated with choroid sclerosis, especially marked at the level of the posterior pole. On the other hand, there are numerous cases of choroid sclerosis which are, in fact, atypical forms of pigmentary degeneration.

Functional symptoms. There is central or pericecal scotoma; the peripheral limits are normal. There is no hemeralopia and no evident disturbance in color sense. The ERG may be normal.

3. Sorsby's Pseudoinflammatory Dystrophy: According to Sorsby's first description, this chorioretinal dystrophy with dominant heredity is not characterized either by concentric narrowing or by hemeralopia. In one of my cases there was an extensive central scotoma, moderate peripheral narrowing (irregular), slow adaptation without subjective hemeralopia, acquired red-green blindness, and a subnormal ERG.

4. Retinopathy with Angioid Streaks: Since Doyne's description of angioid streaks in 1889 these have been found in association with macular degeneration of the exudative senile type (Coppez and Danis), elastic cutaneous pseudoxanthoma (Groenblad and Strandberg syndrome), Paget's disease (Terry syndrome), Ehlers-Danlos disease, and cardiovascular lesions with hypertension due to elastic degeneration of the tunica media of the arteries (Touraine's systemic elastorrhexia). The last-mentioned author regards the affection as a congenital dysembryoplasia, transmitted by an irregular dominant gene.

The mode of affection of the visual function is characteristic.

The photopic field of vision is characterized by a pathognomonic pericecal scotoma, with slight slopes, always more marked at reduced illumination (Goldmann perimeter). There is a slightly sloping central scotoma if a fibrous plaque covers the macular region.

The global threshold of the rods after adaptation is sometimes normal and sometimes subnormal; the curve of adaptation can be very slow.

The scotopic field of vision is always pathological; it is characterized by a pericecal scotoma, more extensive than the photopic pericecal scotoma. The central scotoma in darkness is often markedly pathological and may involve the entire posterior pole. These scotopic anomalies may exist even though the photopic field of vision is completely normal.

The ERG is sometimes normal, sometimes subnormal or negative.

5. Senile Macular Degeneration: Senile macular degeneration is also a hereditary degeneration of the central tapetoretinal part. My familial cases and the direct transmission of the affection from one generation to the other are extremely illustrative in this respect. In the same family different types of senile macular degeneration can be found: the pigmented type, the capillarotic type, and the Coppez-Danis type. This shows that these different types represent fundamentally the same heredodegenerative lesion and need not be differentiated.

Senile macular degeneration is characterized by functional disorders of considerable importance. The photopic field of vision shows a central scotoma with slight slopes, or at least a narrowing of central isopters, as soon as the central visual acuity is affected. The curve of adaptation is affected early; the slowing down of adaptation is characteristic, the terminal threshold being normal or pathological. The scotopic field of vision is characterized by marked hemeralopia of the macular region, which permits of confirming diagnosis in incipient or dubious cases. The ERG often shows

changes: The b wave may be subnormal, and the a wave is sometimes very marked. The ERG is negative or absent in extreme cases.

(C) Uniformity or Polymorphism of Tapetoretinal Degenerations.—The classification of heredofamilial degenerations of the chorioretina is still based on the too artificial conception of a great number of autonomous affections, which are characterized on the basis of the variable ophthalmosopic findings, according to the age of occurrence (congenital, infantile, juvenile, virile, or senile forms) or according to the localization of lesions (choroid atrophy or sclerosis, peripheral or central tapetoretinal degeneration, or cerebroretinal degeneration).

Between all these varieties and subvarieties there are so many intermediary forms, ranging from the simplest to the most complex forms, that the idea of a unique heredodegeneration comes naturally, especially since transitional forms and apparently different types may be found in the same family. Observations have been made on the intrafamilial association of retinitis pigmentosa with retinitis punctata albescens, retinitis pigmentosa with atrophia gyrata and choroideremia, retinitis pigmentosa with abiotrophic choroid sclerosis, retinitis pigmentosa with Stargardt's hereditary macular degeneration, Tay's degeneration with senile macular degeneration, Doyne's degeneration with senile macular degeneration, amaurotic infantile with juvenile idiocy, and others.

The various forms of tapetoretinal degeneration often differ in mode of hereditary transmission; in this respect there is a considerable difference, genetically, between atrophia gyrata and choroideremia, which might otherwise be considered as identical.

The polymorphism is even more marked from a functional point of view. The chief localization of perimetric deficiencies greatly differs from form to form: In typical retinitis pigmentosa it corresponds with equatorial lesions; in retinitis punctata albescens, with diffuse lesions, particularly peripheral, and in central affections, with essentially macular and peripapillary lesions. The only common feature is the fact that the affection is never homogenous throughout all the areas of the field of vision.

The intensity of functional changes, too, is highly variable. They may range from total blindness, as in the terminal stage of peripheral degeneration, to absolute intactness of all functions of vision, as in certain juvenile macular degenerations.

There are considerable differences between the curves of dark adaptation in peripheral degeneration; the curve may be normal, biphasic, biphasic with retarded secondary adaptation and with a normal or subnormal final threshold, or monophasic (low or high). The cone curve seldom shows displacement in time, but often in luminance. In macular heredodegeneration the latter types predominate.

In peripheral tapetoretinal degeneration color vision is characterized by blue-yellow dyschromatopsia, common in nearly all retinal affections, whereas in juvenile macular degeneration red-green blindness may also occur.

The ERG is very polymorphous; it may be normal, subnormal, or absent. If feeble stimuli are used, it is as a rule absent in cases of peripheral degeneration, and it is always absent in true retinitis pigmentosa.

The critical frequency of subjective global fusion is considerably lowered in peripheral degeneration; it may be normal in exclusively macular hereditary degeneration.

The functional polymorphism corresponds with significant histological differences. In chorioretinal abiotrophy the retinal affection in this respect is secondary to the choroid affection, which explains the normal ERG at the onset of atrophia gyrata. The difference between dyschromatopsia acquired in juvenile macular degeneration and that in senile macular degeneration is also based on a difference in the localization of histological lesions.

An important fact from a practical point of view is that the functional polymorphism gives rise to considerable prognostic differences.

TABLE 2.—*Some Interesting Features of the Differential Diagnosis of the Tapetoretinal Degenerations*

	Heredity	Somatic Lesions	EEG	Visual Field	Dark Adaptation	Color Vision	Resting Potential	ERG (Weak Stimuli)
Retinitis pigmentosa	Gen. autosomal recessive; sometimes dom. or sex-linked recessive	Deafness; mental debility; Bardet-Biedl syndrome; ataxic syndromes	Dysrhythmia	Zonular scotoma	Gen. very pathological	Blue-yellow blindness	Gen. subnormal	Absent
Retinitis punctata albescens	Gen. recessive	As above	Dysrhythmia	Concentrical narrowing	Gen. very pathological	Blue-yellow blindness	Gen. subnormal	Normal, subnormal, or absent
Atrophia gyrata, choroidemia, general sclerosis	Atr. gyr., autosomal recessive; choroid., sex-linked recessive	As above	Dysrhythmia	Concentrical narrowing or zonular scotoma	Gen. very pathological	Blue-yellow blindness	Gen. subnormal	Normal, subnormal, or absent
Macular heredodegeneration (Stargardt)	Dominant or autosomal recessive	Idiotic syndromes; Bardet-Biedl syndrome	Dysrhythmia	Central scotoma	Normal or subnormal	Red-green or blue-yellow blindness	Normal	Normal, subnormal, or absent
Sorsby's disease	Dominant			Central scotoma; peripheral contraction	Subnormal		Normal or subnormal	Normal or subnormal
Angioid streaks	Gen. dominant	Groenblad-Strandberg syndrome; Paget's dis.; Ehlers-Danlos dis.; syst. elastorrhexia		Pericecal scotoma; central scotoma	Subnormal		Normal or subnormal	Normal, subnormal, or negative
Senile macular degeneration	Gen. dominant	Vascular dis.	Gen. normal	Central scotoma	Subnormal	Blue-yellow blindness	Normal or subnormal	Normal, subnormal, or negative

The unicist conception of retinal abiotrophies, which seems acceptable for certain genetic reasons (existence in the same family and in the same individual of different types of degeneration), is not completely refutable on the basis of data on functional aspects of vision.

1. The changes in the field of vision have in common that they always affect both photopic and scotopic vision, in contrast with what is seen in the case of purely functional anomalies. Scotopic vision is generally more markedly affected, as shown by a comparison of campimetric findings obtained in light and in darkness.

2. Although the curves of adaptation may show differences, these can all be explained on the basis of the same mechanism of slowing of adaptation, with, consequently, an affection of the final threshold in advanced cases.

3. The ERG changes (more or less parallel diminution in the b and the a wave) constitute a constant characteristic, except in the case of senile macular degeneration. In no case is selective deficiency of one of the components seen, as is the case in functional anomalies (essential hemeralopia, Oguchi disease, achromatopsia, protanopia).

Table 2 gives important features of the differential diagnosis between the chief types of tapetoretinal degeneration.

B. Congenital Functional Anomalies of the Retina

Congenital functional anomalies of the retina (Table 3) are selective, affecting either photopic vision (minor defects of color vision; protanomaly, extreme protanomaly, protanopia, deuteranomaly, extreme deuteranomaly, deuteranopia, tritanomaly, tritanopia, tetartanopia [?]; various forms of congenital achromatopsia) or scotopic vision (Oguchi's disease, essential hemeralopia).

In regard to the differential diagnosis of tapetoretinal degenerations it is obviously

only necessary to discuss achromatopsia and hemeralopia.

(*A*) *Congenital Achromatopsia.*—Complete Congenital Achromatopsia with Amblyopia: This is the form most frequently seen. Some 250 verified cases are on record. The heredity is of the autosomal recessive type. The somatic lesions, which are rare, are dependent on other pathological genes. Objective ocular anomalies may consist either of real but inconstant lesions proper to the affection (mild macular changes or true macular degeneration, pallor of the optic disc, astigmatism) or of common malformations or of changes dependent on other pathological genes (retinitis pigmentosa).

Functional symptoms. The curve of spectral luminosity in photopic vision is almost identical with that obtained in scotopic vision, both in achromatic and in normal subjects. The Purkinje phenomenon is therefore absent, and this is the most characteristic functional manifestation of the affection. Central visual acuity is usually normal in scotopic vision, and, as a rule, far below normal in photopic vision (the curve of distribution formed by photopic central visual acuities in the cases reported has its maximum at 0.1). The peripheral visual acuity regularly improves from the periphery to the paracentral region; in some cases it is considerably above that in normal subjects. The peripheral limits of the photopic field of vision are nearly always normal; the medial region is characterized by marked disorders in spatial summations; in exceptional cases there is an annular scotoma; relative photopic central scotoma exists in some cases but is lacking in other instances. The polymorphism of the affection is again best demonstrated on the basis of the curves of dark adaptation. These may show one of four essential different types: low monophasic, high monophasic, low biphasic, and high biphasic curves. The last-mentioned are the most frequently seen. The final threshold is, as a rule, normal. Contrary to expectations, the macular curves are most often biphasic, with an infranormal absolute threshold. The peripheral thresholds of the scotopic field of vision are normal; on the other hand, the central scotoma in darkness is, as a rule, less dense than in normal subjects and may even be lacking. The resting retinal potential is normal. ERG: After dark adaptation the b_2 wave shows a normal amplitude; the a wave is present; the critical frequency of objective fusion is lowered; the b_1 wave is absent. Binocular vision is often impaired or absent; strabismus is frequently seen. Nystagmus is a classical symptom; it is essentially pendular. The amplitude, direction, conjugation, the effect of surrounding illumination, and fixation differ from case to case. The nystagmus diminishes or disappears toward puberty. The optokinetic reaction is diminished or absent. Photophobia is also a classical symptom. The term is incorrect, because in reality it involves dazzling caused by high brilliance. The size of the pupil in monochromatic light is proportionate to spectral luminosity values. The photopic photomotor reflex is markedly pathological in its mydriatic phase. Histological examinations made by Larsen showed changes in the foveal and parafoveal cones.

It should be pointed out that the selective absence of the b_1 wave is also seen in protanopia and protanomaly.

Incomplete Congenital Achromatopsia with Amblyopia: This condition is very rare (20 cases in literature). If the two extremities of the spectrum are differentiated (with a broad neutral zone between them), the other symptoms are almost identical with those of the form described above.

Congenital Achromatopsia Without Amblyopia: This condition, of which only some 15 cases are on record, as a rule involves complete absence of color perception, but vision is normal or hardly reduced. There is no nystagmus and no photophobia. The curve of spectral luminosity is of the protanopic type or it is deuteranopic (practically normal).

Unilateral Congenital Achromatopsia: This condition is exceptional. The two verified cases in the literature may be regarded as instances of congenital achromatopsia without amblyopia.

(B) Oguchi's Disease.—In this recessive autosomal (or perhaps partly sex-linked) affection the ocular fundus is always pathological, at least after the patient has been exposed to light for a sufficient time. In the majority of cases grayish-white coloration is seen, extremely marked and diffuse but predominantly round the papilla and at the level of the macular region. In some cases there is a yellowish or even a golden-yellow coloration instead of the grayish-white. In some cases the posterior pole is completely normal, while the periphery shows the pathological color. Nearly always the ocular fundus returns to normal after a stay in the dark (Mizuo phenomenon). The affection is always stationary; not the slightest aggravation of objective or functional symptoms has ever been observed.

Functional symptoms. The photopic central visual acuity is normal. The photopic field of vision for white against white is also normal, as is the central color vision. The subjective photopic critical frequency of fusion is considerably lowered. The curve of dark adaptation is biphasic in the majority of cases; secondary adaptation is retarded and diminished in respect to that in normal subjects. The position of the angular point is a function of the previous light adaptation. The resting potential is normal. The ERG is characterized by complete absence of the scotopic b_2 wave; the a wave is highly developed, and the b_1 wave is demonstrable (Fig. 22). The occipital responses to light stimuli are normal.

(C) Essential Hemeralopia.—This condition is characterized by night blindness not associated with any change in the ocular fundus. The diagnosis can therefore not be made with certainty until after examination of the functional syndrome. Hemeralopia does not give rise to disturbance in photopic function, at least as far as central visual acuity, fields of vision, and color sense are concerned. On the other hand, scotopic function is affected to the point of absence of the Purkinje phenomenon. The curve of spectral luminosity in photopic vision is identical with that in scotopic vision; it is similar to the photopic curve in normal subjects. The curve of adaptation does not show α-angulation and is identical with that in foveal vision in normal subjects. The ERG is characteristic: There is selective absence of the positive scotopic component b_2 (Fig. 23).

Essential hemeralopia is always hereditary in nature. It is generally transmitted as a dominant and sometimes as a sex-linked recessive or an autosomal recessive trait. In the last two cases it is associated with myopia.

(D) Oguchi's Disease and Essential Hemeralopia Are Not Tapetoretinal Degenerations.—Numerous authors have con-

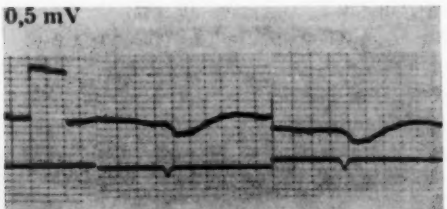

Figure 22

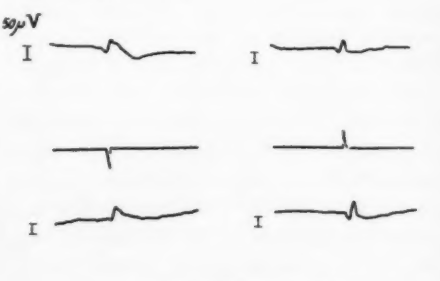

Figure 23

nected Oguchi's disease and essential hemeralopia with retinitis pigmentosa. I disagree with this point of view.

Certain observations tend to suggest the identity of these affections. Coexistence has been reported of apparently essential hemeralopia and peripheral tapetoretinal degeneration in the same family. Yet these observations should be evaluated with great caution. Tapetoretinal degenerations are essentially polymorphous affections, not only in the morphology of their lesions but also in the intensity of changes. In retinitis pigmentosa any of the fundamental signs may be lacking, viz., progressive development, hemeralopia, pigmented spots, grayish discoloration of the ocular fundus, waxy atrophy of the optic disc, thinness of retinal vessels. The simultaneous absence of several of these signs does not imply a genuine essential hemeralopia. The latter is characterized not only by the purity and absolute constancy of its manifestations but also by its congenital and stationary nature. This absence of development is without exception. In fact, the differential diagnosis must not be based on ophthalmoscopic findings but on the functional data, particularly the ERG findings: The a wave may be absent or isolated and the b wave, absent, subnormal, or normal in tapetoretinal degeneration, whereas hemeralopia and Oguchi's disease are characterized absolutely by the selective absence of the b_2 wave.

EEG constitutes another aid in differential diagnosis. Nearly all cases of tapetoretinal degeneration show EEG changes, which are usually lacking in essential hemeralopia and Oguchi's disease.

The majority of observations on "essential hemeralopia" with intrafamilial association of tapetoretinal degeneration are either concerned with cases of mild retinitis pigmentosa or with families with retinitis pigmentosa and, in certain members, still children, hemeralopia without visible lesions of the ocular fundus. In this respect it should be pointed out that Zorn and De Strazzi's cases of "congenital hemeralopia" were subsequently reexamined and found to show unmistakable evidence of retinitis pigmentosa.

The cases which have been regarded as transitional forms of essential congenital hemeralopia and retinitis pigmentosa (sometimes familial, as in the cases described by Ammann) are obviously examples of real tapetoretinal degenerations with a paucity of symptoms.

Congenital hemeralopia has also been connected with progressive choroid sclerosis. Bordley made an interesting observation in this respect. His subjects were a Negro family of 42 members through five generations, of whom 35 were affected by "congenital hemeralopia" complicated, at a later age, by choroid sclerosis and then by neuroparalytic keratitis. No essential hemeralopia seems to have been involved in this material.

Attempts have also been made to connect Oguchi disease with the condition known as "fundus albipunctatus cum hemeralopia." I have had an opportunity to observe typical examples of both affections; functional investigations showed that the albipunctatus fundus is a characteristic tapetoretinal degeneration.

Other investigators have compared retinitis pigmentosa with Oguchi's disease; the two affections may occur in the same family (Oguchi). This is an exceptional fact, however, which may be due to incidental conjunction of two recessive genes.

As to the fundamental dissimilarity with tapetoretinal degenerations, I have absolutely confirmed this only with regard to Oguchi's disease and essential hemeralopia of dominant heredity, which were the only types sufficiently studied from the functional point of view. The various strains of essential dominant hemeralopia seem to be completely identical both in ERG findings and in subjective data. The aberrant ERG findings described by Björk and Karpe and the biphasic curve of adaptation described by Garabedian and Meunier, in fact, indicate nonessential hemeralopia. The ERG find-

TABLE 3.—*Some Interesting Features of the Differential Diagnosis of Congenital Functional Abnormalities of the Retina*

	Heredity	Eye Ground	Photopic Visual Field (Achromatic)	Dark Adaptation	Color Vision	ERG (Neon)
Congenital nonprotanopic partial color defect	Sex-linked recessive	Normal	Normal	Normal	According to type	Normal
Congenital protanopic partial color defect	Sex-linked recessive	Normal	Normal but practically absent for red	Nearly normal	According to type	No b_1 wave (apparently)
Typical achromatopsia	Autosomal recessive	Macular lesions	Trouble spat. somm.; practically absent for red	Nearly normal	According to type	No b_1 wave (apparently)
Oguchi's disease	Autosomal recessive	White or yellow color	Normal	Secondary adaptation retarded & subnormal	Normal	No b_2 wave
Essential hemeralopia	Dominant, autosomal recessive, sex-linked recessive	Normal	Normal	Secondary adaptation absent	Normal	No b_2 wave

ings obtained by Riggs resemble mine, but the interpretation differs.

The fact that no case of essential hemeralopia with myopia has ever been submitted to a thorough functional examination is unfortunate, not in the least because simple myopia itself is often associated with mild hemeralopia. In any case, at least an ERG should be made before it can be concluded that hemeralopia of dominant heredity and that associated with myopia (recessive sex-linked or autosomal heredity) are identical.

Table 3 shows some important points of the differential diagnosis between several congenital functional abnormalities of the retina.

C. Congenital Chorioretinitis

The most important causes of congenital chorioretinitis are syphilis and rubella.

(A) Syphilitic Congenital Chorioretinitis. According to Sidler-Huguenin and Troncoso, the following types of heredosyphilitic chorioretinitis can be distinguished:

Type I: The periphery of the ocular fundus presents numerous yellowish spots, well circumscribed and with a diameter of ⅛ to 1/20 p. d. Innumerable small black dots are seen in between the yellowish spots (pepper-and-salt aspect).

Type II: The pigmentary spots are larger and sometimes have the shape of osseous corpuscles. The yellow spots may have a central black point; they are found as far as the proximity of the posterior pole. The entire fundus can have a colorless appearance. The optic disc is pale, and its limits are sharp or blurred. The retinal vessels are thin; there may be perivasculitis. The central vision is often diminished. The field of vision often shows peripheral narrowing; hemeralopia is sometimes recorded.

Type III (the Coarse Spotted Form): The lesions start with white or yellow spots, not sharply circumscribed and fairly large; the development is characterized by large pigmentary mass formation with notched outlines, localized between the ora serrata and the equator. Pigmentations are sometimes perivascular. The retina often showed a bluish color; the papilla is, as a rule, normal. Central vision is seldom affected; the field of vision may be narrowed. This type is very frequently seen and is, as a rule, bilateral.

Type IV (Syphilitic Retinitis Pigmentosa): Pigmentation is characterized by osseous corpuscles found in the entire periphery of the ocular fundus; as in the case of idiopathic retinitis pigmentosa the pigments are sometimes perivascular. There are often round black spots near the papilla, separated by round yellow spots surrounded by a black network. The retina is often bluish; the optic disc is yellow, and the retinal vessels are narrowed. The choroid vessels are either normal or sclerotic. Central vision is diminished; the field of vision

is characterized by annular scotoma. The condition is sometimes stationary and in other cases progressive.

Summarizing the various symptoms which enable us to differentiate chorioretinitis from retinitis pigmentosa, the following facts should be considered: (1) signs of posterior or anterior uveitis (spots of choroiditis, opacity of the vitreous body, posterior synechiae) and signs of parenchymal keratitis; (2) the degree of periarteritis and endarteritis; (3) the atypical character of retinal pigmentation (peripapillary rounded masses, atrophic plaques); (4) early atrophy of the optic nerve; (5) diminution of central vision not in agreement with the degree of narrowing of the field of vision; (6) a positive b wave in the ERG; (7) successful specific treatment. The serological results are also significant if they are positive.

(B) Rubellar Congenital Chorioretinitis.—It should be borne in mind that rubellar embryopathies generally occur if the mother is infected within the first three months of pregnancy; three organs are selectively affected in about 50% of cases, viz., the eye, the internal ear, and the heart. The eye and the internal ear are seldom affected simultaneously; the eye and the heart, however, are often affected together. The cranium and the encephalon are affected in 15% of cases, and the teeth, in at least 3%.

Three of the ocular anomalies observed are particularly frequent, viz., cataract, microphthalmia, and retinal dystrophy.

Retinal dystrophy is very frequently seen, especially if the fact is taken into account that it is often masked by cataract. It is observed in more than one-third of cases of rubellar embryopathy. It is characterized by disseminated pigmented spots, especially marked at the level of the posterior pole, or by a finely grained pigmentation associated with lacunar yellowish spots. Waxy atrophy of the optic disc may exist.

The function of the eye does not seem to be disturbed in the majority of cases, where verification is possible, as in one of my cases (Fig. 24). The ERG, the field of vision, the curve of dark adaptation, and color perception were all normal.

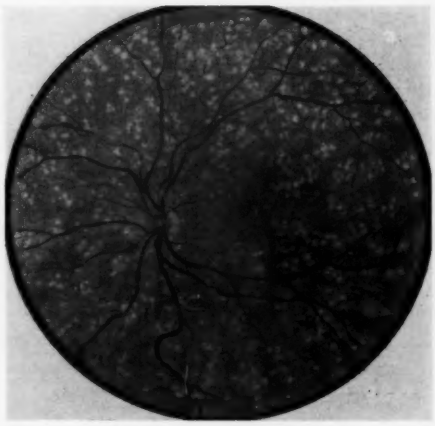

Figure 24

(C) Congenital Chorioretinitis of Other Etiologies.—Embryopathies are attributed to viral causes other than rubella, viz., mumps, varicella, poliomyelitis, infectious hepatitis, measles, scarlatina, influenza, herpes zoster, etc. In view of the fact that these diseases are more frequently seen in pregnant women than rubella, while the number of embryopathies attributable to them is lower, their etiological importance has not been established beyond doubt. According to Küntzel, only mumps, poliomyelitis, influenza, and infectious hepatitis may be involved. The clinical symptoms of such viral embryopathies are apparently identical with those of the embryopathy caused by rubella; the number of cases reported is not sufficiently large to determine valuable statistical differences.

Some investigators maintain that an embryopathy may also originate from certain nonviral maternal affections (septicemia and nephritis) or even from noninfectious affections of the mother (allergy, hypertension, diabetes, and metabolic disorders). This has not hitherto been demonstrated.

In exceptional cases toxoplasmosis may give rise to pseudo-retinitis-pigmentosa instead of the necrotic macular type of chorioretinitis which is pathognomonic.

D. Acquired Chorioretinitis

Acquired chorioretinitis, which should be differentiated from tapetoretinal degeneration, includes certain forms of syphilitic chorioretinitis and secondary retinitis pigmentosa.

The morphological aspect of cicatricial syphilitic chorioretinitis can be very similar to that of idiopathic retinitis pigmentosa. There may be thinness of the retinal vessels and waxy atrophy of the optic disc, annular scotoma, and changes in light sense. Special attention should be given to vitreous opacity, peripheral narrowing of the field of vision, and, especially, the presence of a b wave in the ERG. These are the important factors to be used in differential diagnosis.

Secondary retinitis pigmentosa may be of highly variable etiology; possible etiological factors include trauma, siderosis, retinal cysts, intoxication, myopia, vaccination, measles, parotitis epidemica, epidemic encephalitis, malaria, typhoid fever, scarlet fever, diphtheria, and Kimmelstiel's disease. The ophthalmoscopic findings may be completely identical with those of idiopathic retinitis pigmentosa, but the pathological anatomical features are different.

In the primary form the degenerative process is primarily localized in the neuroepithelium. It first affects the rods, the external segment of which degenerates and then disappears; the external limiting membrane subsequently merges with the pigmentary epithelium, after which the external grains degenerate. In the secondary form, on the other hand, there are no primary lesions of the sensory cells of the neuroepithelium; it is sclerosis and obliteration of the cells of the retinal vessels which give rise to localized retinal destructions. Analogous lesions exist at the level of the choroid vessels, but the subjacent pigmentary epithelium and neuroepithelium are secondarily affected and much later. Yet there remain zones in which the sensory cells of the neuroepithelium are well preserved (Blum and Babel).

There are no marked differences between the hereditary and the acquired degenerations as regards affection of visual function. Relative scotoma is first seen in both groups, followed by absolute scotoma, more extensive in scotopic vision. Dark adaptation is retarded, and the ERG shows more or less marked changes.

It should be pointed out, however, that adaptation is relatively less affected in chorioretinitis than in tapetoretinal degeneration and that electroretinography remains an important aid in differential diagnosis. In genuine retinitis pigmentosa positive components of the ERG are generally absent, from the onset of the affection and sometimes even from birth onward. In pseudo retinitis pigmentosa, on the other hand, it is generally positive, if subnormal. In diffuse choroiditis it does not disappear until the terminal stage.

If there is no essential difference between the affection of visual function in degenerative affections and that in acquired affections, there is an important difference in the quantitative expression of disturbances, at least in relation to peripheral hereditary degeneration. The functional affection is in fact more complete in genuine retinitis pigmentosa than in pseudo forms, in that the adaptation of the rods and the ERG b waves completely disappear in the former, whereas they are often only diminished in the latter conditions.

It should also be pointed out that acquired localized cicatricial chorioretinitis does not give rise to any disturbance in global dark adaptation, nor does it cause any change in the base value of the electro-oculogram and the ERG.

4. Particularly Difficult Cases

(A) Achromatopsia Associated with Tapetoretinal Degeneration.—The achromatopsia observed in association with peripheral tapetoretinal degeneration is highly variable in its nature.

In the first type the dyschromatopsia is wholly acquired and originates in a confusion

in a blue-yellow axis; it is subsequently complicated progressively by red-green amblyopia which finally leads to achromatopsia with a spectral luminosity curve of the photopic type.

In the second type there is, in addition to tapetoretinal degeneration, congenital dyschromatopsia (protanopia or deuteranopia); this, associated with acquired blue-yellow blindness, gives rise to achromatopsia with a spectral luminosity curve of the photopic type.

In the third type there is a linkage between the retinitis pigmentosa and the congenital achromatopsia, as both depend on recessive genes. This form of achromatopsia can be recognized by the scotopic type of curve of spectral luminosity.

Central tapetoretinal degenerations can also give rise to achromatopsia, which is easily differentiated from congenital achromatopsia with macular lesions on the basis of normal color sense in the peripheral retinal regions.

The following observation on juvenile macular degeneration with predominant affection of photopic vision is an example.

In this patient the Stargardt type of juvenile macular degeneration existed since the age of 15 years. The affection was bilateral and slowly progressive. The maculae showed degenerative changes, the nature of which was confirmed by certain functional signs, viz., delayed adaptation, a subnormal ERG response, and diffuse affection of the brain as shown by EEG findings.

Other functional signs were considerably less typical of Stargardts' disease. The central scotopic field of vision was considerably less affected than the central photopic field of vision. On the other hand, there was exclusively central complete achromatopsia with a spectral luminosity curve of the scotopic type. These two symptoms showed a predominant affection of the cones.

(B) Central and Pericentral Retinitis Pigmentosa.—The diagnosis of pigmentary degeneration localized to the macular region or the perimacular region offers no great difficulty if the ophthalmoscopic aspect of the lesions is characteristic and if star-shaped pigmentations in the form of osteoblasts exist. This, however, is not always the case, as shown by the following example.

The patient was a man whose sister showed typical retinitis pigmentosa with superimposed macular degeneration. Since the age of 17 his central vision had progressively diminished; yet he did not feel impaired in his movements, and there was no hemeralopia. On the contrary, the impression was that his sight was better in less bright light. Adaptation was unfortunately not determined.

The visual acuity was reduced to 0.1 in both eyes. The peripheral field of vision was absolutely complete.

Both eyes showed characteristic macular degeneration in the form of a regularly rounded focus of about 1½ p. d., which was much clearer than the remainder of the retina. At this level the pigmentary epithelium was atrophic, the only thing remaining being a very fine gray scattered dust; the choroid vessels were apparent and normal. The outline of the focus of degeneration was clearly marked and intensively pigmented. Round the altered macular region the retina retained its red color and its usual aspect. The optic papillae were normal, but the retinal vessels were slightly narrowed. The equatorial part of the retina showed a pepper-and-salt appearance against a metallic gray background; there was an occasional pigmented spot, atrophic areas, and sometimes a mass of a few yellowish dots. In no place were pigmentary granules seen, except on the right side, where an elongated pigmentary spot was seen along a vessel, above the optic disc.

The ERG showed no apparent retinal response, a fact which led to the conclusion that Stargardt's disease was not involved, but rather an atypical pigmentary degeneration of the retina, whereas the patient's sister showed a characteristic retinitis pigmentosa.

The following is another observation, which it may be interesting to compare with the previous one.

A girl aged 19, whose brother showed typical retinitis pigmentosa, showed macular degeneration (small brown-reddish spots and a varnished and snail slime appearance). The posterior pole was surrounded by a garland, showing also complete aplasia of the pigmentary epithelium and an accumulation of pigment of the osteoblast type. This garland was only interrupted below and on the nasal side, where numerous small yellowish spots were seen. From the garland on to the extreme periphery the retina appeared to be normal.

Vision was below 0.1 in both eyes. The field of vision in both eyes showed a large scotoma with slight slopes and a morphology reminiscent of that of an annular scotoma. This scotoma involved the point of fixation and was open upward. The peripheral limits were normal. Adaptometry revealed an extremely pathological curve in spite of the lack of subjective hemeralopia. ERG examination showed a normal response in the right eye and a supranormal one in the left eye.

In this case the diagnosis of retinitis pigmentosa is based not only on the genetic data but also on the ophthalmoscopic findings and the typical changes in the field of vision. In view of the fact that the ERG was normal, the conclusion can be formed that the affection is strictly localized and, therefore, has a favorable prognosis.

The following is another case of pericentral tapetoretinal degeneration: A woman aged 33 showed whitish perimacular punctates in both eyes, which corresponded with hemeralopigenic changes in the field of vision. The color sense showed a beginning of blue-yellow blindness; the curve of dark adaptation and the ERG were normal.

(C) Senile Retinitis Pigmentosa.—Various authors have reported retinitis pigmentosa beginning at a very advanced age; in such cases the choroid sclerosis was considerably more marked than the retinal pigmentation. The question arose as to whether this was a condition of vascular origin or a genuine tapetoretinal degeneration.

The following are two observations of senile retinitis pigmentosa.

Case 1.—A man aged 71 sought advice in 1951 for diminished vision which had started about three years previously. The vision was still 0.4 in the right eye and 0.6 in the left, both eyes showing a concentric narrowing of the field of vision to 10 degrees. Examination of the ocular fundus showed a pallor of the optic disc with slightly blurred outline; the retinal arteries and veins were very thin and disappeared at the level of the peripheral region.

In February, 1954, the ocular fundus of both eyes (Fig. 25) showed a primitive optic atrophy; the retinal vessels were filiform; only the temporal vessels could be followed over a distance of 4 p. d.; the retina seemed to be avascular outside the posterior pole, and the arterial as well as the venous tree was atrophied. The macular region showed a homogeneous aspect and brownish discoloration without any marked changes. There was atrophy of the pigmentary epithelium, through which markedly sclerotic choroid vessels were visible. At the level of the superointernal quadrant of the retina a few small accumulations of pigment were found in both eyes.

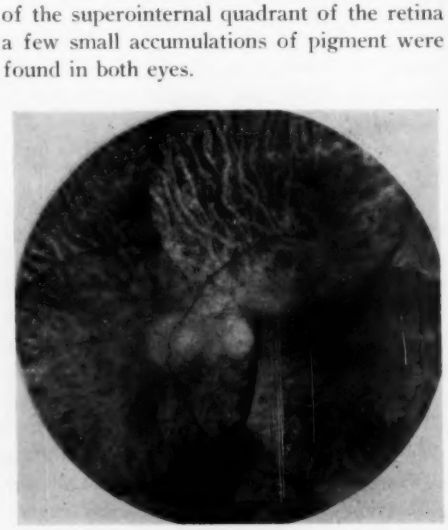

Figure 25

Visual acuity was below 0.1 on the right and 0.4 on the left. The field of vision was concentrically constricted to 5 degrees on both sides. The curve of adaptation was extremely pathological, and the ERG showed absence of any retinal response. The EEG showed a not very regular α rhythm of 11 to 12 cps and 15μv. to 25μv. In the occipital and temporo-occipital regions there were waves of 4 to 6 cps. There were also pike-shaped waves, especially in the temporal and parieto-occipital regions. There were no signs of localization. The α-blocking was hardly noticeable, and there were no changes during intermittent light stimulation. Hyperpnea caused only slight changes.

Thorough general examination yielded no particular information; the Wassermann test was negative. There was no similar case in the family. The patient had had no severe infectious disease.

CASE 2.—A man aged 65 complained of bumping into objects, which had begun three years previously.

The ocular fundi showed buff-colored papillae with blurred limits; the retinal vessels were thin and rarefied; the vascular tree seemed to be reduced to the chief branches. The macula was dappled in a brownish color. The retinal periphery showed a pepper-and-salt aspect, and the choroid vessels, glimpses of which were visible, were sclerotic. There were no pigmentations of osteoblast type, but, at the level of the nasal superior quadrant in the two eyes, there were a few small accumulations of pigment.

Visual acuity was 0.7 on the right and 0.8 on the left. The field of vision was concentrically constricted to 5 degrees on both sides. The curve of dark adaptation was clearly delayed. ERG examination showed no retinal response. EEG examination yielded a low voltage symmetric record with a regular α rhythm.

The absence of the ERG response showed that, in these two cases, there was a true tapetoretinal degeneration; the EEG findings in one case were identical with those found in the majority of cases of retinitis pigmentosa.

(D) Abortive Forms of Retinitis Pigmentosa.—It has been pointed out that the so-called "essential hemeralopia" observed in families affected with retinitis pigmentosa is in fact a tapetoretinal degeneration with a paucity of symptoms. The following observation confirms this opinion.

The patients were a man aged 51, and his two sons, aged 25 and 19. The man and the elder son showed absolutely typical retinitis pigmentosa, both ophthalmoscopically and as regards functional findings: field of vision with annular scotoma, curve of dark adaptation highly pathological, ERG absent, EEG with typical changes; specific occipital response absent or retarded.

The younger son showed only mild aspecific peripheral chorioretinitis; small yellowish spots, hardly visible, and two to three small accumulations of punctiform pigments. The fields of vision only showed a depression of the middle isopters. The curve of dark adaptation was subnormal. The ERG response, although subnormal, was positive; there was an evident b_1 and a b_2 wave. The EEG was normal, as was the specific occipital response. A favorable prognosis was accepted in this case.

Whereas the father showed marked acquired dyschromatopsia of the blue-yellow axis, the son suffering from the abortive form showed congenital deuteranomaly, and the other son, with typical retinitis pigmentosa, apparently deuteranopia; this was perhaps an aggravation of a congenital deuteranomaly.

This observation on "abortive" retinitis pigmentosa also illustrates the mild character of retinitis pigmentosa of dominant heredity.

The following are two other observations on abortive retinitis pigmentosa.

A boy aged 15 complained of diminished vision and hemeralopia. He had become obese within a few years and showed mediocre intelligence (he found it difficult to keep abreast of his class). The physical

as well as the mental condition was attributed to thyroid insufficiency. He was an only son. The parents were second cousins.

Vision, after correction of myopic astigmatism, was 0.5 in both eyes. The field of vision showed mild concentric constriction. There was marked hemeralopia. Examination of the ocular fundus showed a normal papilla; the retinal vessels showed no change, and the macular region was intact. The retinal periphery showed the aspect of heredospecific chorioretinitis, characterized by the presence of a few pigmentary spots of variable form and dimension against a slate gray background.

The patient showed the Froehlich type of obesity, hypogenitalism, mental deficiency, and certain metabolic disturbances.

The consanguinity of the ascendants and signs of a Bardet-Biedl syndrome made it possible to diagnose the condition as abortive retinitis pigmentosa.

The second observation is concerned with a woman at present aged 21. The posterior pole of the ocular fundus showed, in both eyes, depigmented spots of yellowish color in the retrovascular region, without a sharply circumscribed outline (irregular, interrupted contours) of variable dimensions but nearly always small. It was covered by a fine layer of pigmentary dust, which was thicker near the spots, which it accentuated. Some of the spots were very clear, and some were atrophic, of gray-whitish color. The latter, which were more numerous in the right eye, had larger and more marked pigmentations at their margins. The macular region showed dark discoloration caused by a dense pigmentary dust, gray-blackish in color, which occupied the spaces left untouched by the depigmented spots. The extreme periphery of the retina showed a granular aspect of the pepper-and-salt type, irregularly covered by a fine dust of pigment, against a more or less colorless background through which choroid vessels of normal appearance were visible. There were more or less extensive plaques showing marked atrophy, where more voluminous pigment granules were seen, here and there accumulating to a mass. The discs and the retinal vessels were normal.

There was no other ocular anomaly and no dyschromatopsia. The visual acuity was 10/10 in both eyes after correction of a myopia of 3.50 D. The field of vision was normal in both eyes. There was no hemeralopia.

At the end of 10 years the ocular fundus was still unchanged. Visual acuity was still 1.0, and the field of vision was still complete; light sense was intact.

This was not a case of inflammatory chorioretinitis but rather one of a curious form of retinal degeneration, particularly of the pigmentary epithelium, while a second cousin of the patient showed a characteristic retinitis pigmentosa.

These facts have led us to form a number of important conclusions: 1. One should never rely on a simple interrogation as to the number of tapetoretinal degenerations existing in the same family nor as to the conclusion that a case is an isolated instance; although exceptional, there are cases of degeneration not associated with any apparent functional disorder. 2. Abiotrophy of the retinal neuroepithelium may show very different ophthalmoscopic features, as the same genetic constitution may produce highly variable phenotypical manifestations. 3. In retinitis pigmentosa as well as in tapetoretinal degeneration the capital fact is not the retinal pigmentation by any means; the real characteristic is the degeneration of the pigmentary epithelium, this is followed by degeneration of sensory elements.

(E) Apparently Acquired Idiopathic Retinitis Pigmentosa and Apparently Abiotrophic Secondary Retinitis Pigmentosa.—It has been Sorby's merit to emphasize that tapetoretinal degeneration may have all the ophthalmoscopic characteristics of inflammatory chorioretinitis.

The following is an illustrative observation.

A woman aged 35 lost vision in the left eye 12 years previously; for a few months she has been complaining of disturbances in vision in the right eye. At the level of the posterior pole this eye showed chorioretinitis of the degenerative type; the left eye showed the features of diffuse cicatricial heavily pigmented chorioretinitis.

Visual acuity in the right eye was 0.1; that in the left eye was reduced to perception of movements of the hands. Both fields of vision showed a large central scotoma; in the right eye the large-object tests made it possible to separate two islets in this scotoma. Adaptometry yielded a subnormal biphasic curve. The diagnosis of atypical tapetoretinal degeneration was confirmed by the absence of an ERG response and by the EEG changes, which were typical of abiotrophy (diffuse dysrhythmia and polymorphism of very low voltage and without fronto-occipital differentiation).

The following are a few observations on retinitis pigmentosa with primary aspects but in reality of secondary nature.

A woman aged 58 lost vision in the left eye following two operations. The right eye showed the sequelae of an old uveitis with peripheral iridectomy, papillary seclusion, subluxation of the crystalline lens, and vitreous changes, but there was also a retinitis pigmentosa of the classical type, with constriction of retinal vessels and atrophy of the optic nerve.

The visual acuity was 0.1. The field of vision was constricted to 20 to 30 degrees. The curve of dark adaptation was subnormal. The color sense was reduced, but the dyschromatopsia showed no definite axis. The base value of the EOG was very pathological (25μv. to 30μv.). The ERG was subnormal but positive (amplitude of the b wave 50μv. for 0.2 joule xenon light).

In this case the field of vision, the color sense, and especially the ERG showed the secondary nature of the retinal changes.

A boy at present aged 15 showed, at the age of 8, chronic bilateral retrobulbar neuritis, the cause of which has never been established. Despite various therapies the central scotoma persisted, although the peripheral field of vision remained complete. Five years later there were changes in the ocular fundus only too readily confused with those seen in retinitis pigmentosa. The optic discs were slightly pale on the temporal side; the macular region seemed varnished; the entire peripheral retina was occupied by irregular pigments and ramified in the form of osteoblasts; the retinal vessels were normal.

The ERG was positive, if subnormal (amplitude of the b wave 200μv. by the Karpe technique). This showed that the case did not involve true retinitis pigmentosa but a secondary degeneration.

A girl aged 8 showed acute amaurosis in the course of measles. This was followed by retinitis of the pigmentary type, while vision at the same time improved. The field of vision showed a moderate depression. At the first recording the ERG was absent on both sides, but subsequently an electronegative response was obtained (Fig. 26), which confirmed the diagnosis of morbillous pseudo-retinitis-pigmentosa, in view of the fact that, with the Karpe technique, the ERG never shows the slightest response in idiopathic retinitis pigmentosa.

Finally, I present two observations on syphilitic pseudo-retinitis-pigmentosa, which were also diagnosed on the basis of ERG findings.

A man aged 58 had suffered since the age of 16 years from diminished vision. He was being treated for retinitis pigmentosa. In fact there was diffuse bilateral chorioretinitis with pigmentary migration

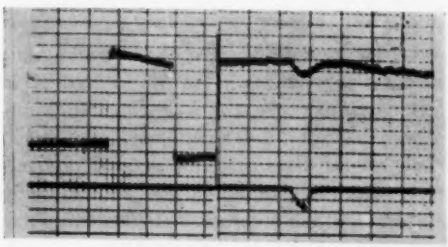

Figure 26

especially marked at the level of the macular region and choroid sclerosis. The discs and the retinal vessels were normal. The Wassermann reaction was positive.

Central vision acuity was reduced to 1/20 (right eye) and 1/5 (left eye). The right field of vision showed an enormous central scotoma of 20 degrees at the 3/4 test and 35 degrees at the 2/4 test (Goldmann perimeter). There was no concentric narrowing. The left eye showed an annular scotoma in the temporal half of the field and a very deep notch in all isopters of the inferior nasal quadrant; there was no concentric narrowing. Adaptometry on global thresholds showed a normal curve, and the ERG response was positive but very subnormal in both eyes (amplitude of the b wave 30μv. on the right and 40μv. on the left; Karpe technique).

A woman aged 65 was suffering from syphilis, with a positive Wassermann reaction. Ophthalmoscopic examination showed the typical features of retinitis pigmentosa without demonstrable macular lesions.

Visual acuity was 1/40 in both eyes. The fields of vision showed annular scotomata. Adaptometry yielded highly abnormal biphasic curves. ERG showed no response to isolated stimuli but very slight fluctuating response to intermittent stimulation.

(F) Unilateral Retinitis Pigmentosa.—The hereditary and abiotrophic nature of idiopathic retinitis pigmentosa is not incompatible with a unilateral localization. These cases may either involve an exceptional manifestation of a recessive gene in a heterozygotic state (Maeder and Müller) or a genotypical asymmetry in the sense introduced by Dahlberg, or heredity *en mosaïque*.

If the hypothesis of unilateral idiopathic retinitis pigmentosa is to be forwarded in any particular case, the following conditions should be met: 1. The affected eye should show all the classical symptoms of pigmentary retinal degeneration, viz., characteristic features of the ocular fundus, annular scotoma, hemeralopia, absent ERG to weak stimuli. 2. The presumably unaffected eye should not show even a masked sign of the condition; nor should there be changes in the field of vision or in the dark adaptation, nor ERG changes. 3. The period of observation should be sufficiently prolonged (more than five years) to exclude a retarded affection of the contralateral eye. 4. There should be no sign of a general affection such as syphilis, which might produce retinal lesions resembling those of retinitis pigmentosa.

Taking these criteria into account, I have come across in the literature 25 authentic cases of unilateral retinitis pigmentosa. Yet there should still be some reserve, as only 10 of these cases have been followed for a period exceeding five years.

I have had occasion to follow for 20 years a typical and certain case of unilateral retinitis pigmentosa, which showed the following features:

The right eye showed a pseudocoloboma of the macula without any sign of retinitis pigmentosa. Ophthalmoscopic findings were negative from this point of view. The peripheral field of vision was complete; the color sense was intact; dark adaptation was normal, as was the ERG and the fall in the EOG during dark adaptation.

The left eye showed an absolutely characteristic pigmentary degeneration of the retina; central visual acuity was reduced to 0.3; the field of vision was concentrically constricted to 10 degrees; dark adaptation was markedly pathological, and the ERG was absent; there was no fall in EOG during dark adaptation, and the basic value of the EOG was considerably lower than that in the contralateral eye.

Unilateral retinitis pigmentosa therefore really exists. An analysis of the observations so far published reveals three striking facts: 1. The age of occurrence is often later in life. 2. There is complete or partial deafness in at least 10% of cases of retinitis pigmentosa. Yet in the "authentic" unilateral cases degenerative auditory disturbances have been reported only twice. 3. The

classical form of retinitis pigmentosa is manifestly familial and hereditary. This is not the case in unilateral retinitis pigmentosa. Consanguinity has been investigated in 27 cases but established in only 3; heredity was investigated in 26 cases and demonstrated in 5 (dubious otherwise).

Therefore, it is an open question if there are cases of unilateral retinitis pigmentosa which are truly equivalent to bilateral cases.

(G) Ocular Lesions Associated with Obesity and Hypogenitalism.—Besides obesity with hypogenitalism due to tumoral lesions, infections, traumata, or prepuberal functional disorders in the diencephalohypophyseal region (Babinski-Froehlich's adiposogenital dystrophy or pseudo-Froehlich syndrome), there are genotypical adiposogenital syndromes of degenerative origin, generally associated with ocular lesions; the Bardet-Biedl syndrome is the commonest of these conditions.

In this condition the retinitis pigmentosa is sometimes replaced by "pigmentary retinopathy without pigment" or by apigmentary hemeralopic degeneration. Other equivalents are known, e. g., optic atrophy, coloboma of the iris, or external ophthalmoplegia.

The following case is even more exceptional.

The patient was a boy aged 14, with lesions of the ocular fundus reminiscent of those seen in amaurotic idiocy. The posterior pole was grayish. This anomalous color, progressively softening to the periphery, affected the macular as well as the peripapillary region. The fovea stood out clearly and appeared to be punctuated by microscopic red spots. The optic disc was pink and nonatrophic; its outline was slightly blurred. The retinal vessels were normal. The peripheral parts of the ocular fundus showed no anomaly. In view of the mental condition of the patient, visual acuity could not be determined nor could the field of vision. In any case, the patient moved without difficulty and recognized objects presented to him with either eye.

The ERG in the right eye showed a positive response of normal amplitude, which excluded tapetoretinal degeneration of the retinitis pigmentosa type.

The patient had had epileptic convulsions since the age of 2 years, which progressively increased in frequency from the age of 6 on. There was obesity of the cerebral type, which seemed congenital and was markedly aggravated at the age of 8. Facts recorded included a double Babinski sign and hollow feet. Hypogenitalism (very small penis) was associated with hirsutism and the development, satisfactory for the age, of secondary sex characters (beard). There was progressive mental regression. EEG findings led to the conclusion that a diffuse encephalopathic process with basal predominance and a epileptic component existed. No pituitary insufficiency was demonstrated.

There seemed to be an unusually high percentage of constitutional obesity in the family. On the other hand, a brother and a sister showed convulsions until the age of 2 years.

It is evidently difficult to classify this case; without an anatomical investigation we must resort to hypotheses. The subject showed the general morphology of cerebral obesity, of which the boy showed the typical dissociated genital disorders. There was certainly no genetic argument in favor of another classification than that of obesity with hypogenitalism of cerebral origin. Yet three important factors made us hesitate as to the related Bardet-Biedl syndrome: 1. In cerebral obesity the development is considerably slower and more torpid. 2. The mental disturbances in this patient are not definitely those usually seen in cerebral obesity. Bardet-Biedl's and related syndromes are mainly oligophrenic; in this case, however, the mental changes were considerably more marked; there was progressive organic dementia. 3. Degenerative cerebral obesity usually shows no comitial manifestations, or only a few, and the EEG

changes are different from those as a rule seen in Bardet-Biedl's syndrome.

My final diagnosis was an "atypical form of juvenile amaurotic idiocy."

The second point to which I wish to draw attention is that of the mild ocular symptoms observed in the Froehlich and the pseudo-Froehlich syndromes.

I have been able to examine a young man with retarded puberty. Whereas the ocular fundi, visual acuity, curve of dark adaptation, and base EOG value were completely normal, the ERG was considerably subnormal, as was the fall in the EOG during dark adaptation.

Other investigators have described changes in the subjective curve of dark adaptation in adiposogenital syndromes.

Do these cases involve abortive tapetoretinal degeneration or secondary functional lesions or neurohypophyseal dysfunction?

(H) Idiopathic and Secondary Hemeralopia.—Three chief forms of hemeralopia can be distinguished, viz., (1) essential hemeralopia, characterized by the presence of a hereditary factor, by a congenital and stationary character, by a completely normal ocular fundus, and by an ERG showing selective absence of the positive scotopic component; (2) deficiency hemeralopia, characterized by absence of heredity, an acquired nature, and susceptibility to aggravation or improvement, sometimes by the presence of extraretinal lesions, avitaminosis, and absence of the ERG; (3) hemeralopia secondary to sometimes hereditary retinal lesions, characterized by changes in the ocular fundus, an acquired and progressive nature, and an ERG which may be absent or present but which shows no selective absence of the positive scotopic component.

There are other types besides these extreme forms. I have mentioned false essential hemeralopia due to tapetoretinal degeneration with a paucity of symptoms and disturbances in adaptation associated with adiposogenital syndromes.

Summary

The differential diagnosis of peripheral and central tapetoretinal degenerations, congenital functional anomalies of the retina, and congenital and acquired chorioretinitis is discussed, and some particularly difficult cases are described.

2 Avenue Pasteur.

Annual Reviews

Lids, Lacrimal Apparatus, and Conjunctiva

CROWELL BEARD, M.D., San Jose, Calif.

Introduction

This year, as in the previous review, I shall attempt to summarize what seem to me to be the more important contributions in that part of the world literature which is available to me. For an article of this type to be moderately readable some editorial comment must be included. Consequently, many of my own ideas will find their way into the text. Should they be at variance with those of the author of the quoted article or of the reader, it should be remembered that it is difference of opinion which makes horse racing America's leading spectator sport. I may drop back into the previous year to pick up occasional articles which have come to my attention since the previous year's deadline. As in every year, the literature is so voluminous that all contributions cannot—and should not—be cited. I believe that any author worthy of being cited should be named in the text as well as in the bibliography, and this will be done. Many worthwhile articles will doubtless be overlooked. Last year it was my hope that the reader would profit a fraction as much by reading the review as I had by preparing it. This year I have the same hope—but even more so: I hope that the title is correct for the final printing. I am interested in the lips but hardly an authority on them.

Lids

Ptosis.—One of the more difficult problems in ophthalmic surgery is the correction of the ptotic eyelid. The use of fascia lata as a frontalis sling has been recommended by Crawford.[1] He presents the technique for removal of the fascia strips and some refinements in placing them to elevate the lid. These changes are most certainly an improvement over older methods of placing fascia lata. Crawford says that the early lagophthalmos during sleep and the "suspended" appearance of the eyelid gradually disappear and that the patient is able to raise and lower the eyelid well as he learns to control the frontalis muscle. He states that at the Hospital for Sick Children in Toronto a much higher percentage of satisfactory results was obtained in ptosis repair when fascia lata was used than with any other method of repair. The startling thing was that this applied to all types of ptosis, even those with good levator action. In the discussion of Crawford's paper Berke states, ". . . this type of operation should not be indicated for all types of ptosis. I think it should be reserved for cases in which resection of the levator is contraindicated or has resulted in failure. In this connection it should be added that as we grow in experience with the operation for shortening the levator muscle, we find fewer and fewer cases that result in failure."

Philps[2] states that the best results in ptosis are obtained from levator shortening even when there is no evidence of any action in this muscle. He uses a skin approach in isolating the muscle. More articles aimed at popularizing levator shortening are needed, as many surgeons tend to drift away from its use.

With regard to fascia lata, the Dickey operation has been resurrected by Law.[3] There are not many indications for use of

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the superior rectus in the correction of ptosis. In this regard I have Dr. Dickey's permission to quote him as saying that he no longer uses the "Dickey operation." He feels that there are other superior rectus procedures which result in fewer postoperative complications.

Bettman [4] presents a modification of the Friedenwald-Guyton sling operation. Many surgeons have ceased using this operation because of late infections. Bettman believes that many of these are due to the suture being anchored close to the lid margin, leading to access of bacteria to the suture tract. He advocates anchoring the suture to the upper part of the tarsus with additional buried sutures and describes his technique in detail. It seems to be a definite improvement over the original technique.

Hervouet and Tessier [5] presented a new idea in ptosis surgery. They call attention to the normal antagonism which exists between the orbicularis palpebrae and the levator. They do a partial tarsectomy and levator shortening and in addition make a skin incision and remove a considerable portion of the orbicularis muscle overlying the tarsus and orbital septum. In this way, they feel, the effect of the levator shortening is enhanced.

Simpson [6] reported an interesting and unusual case wherein a patient with ptosis, an exotropia, and a hypotropia of one eye was treated with (1) a resection of the medial rectus and a tenotomy of the lateral rectus, (2) a resection of the superior rectus and a recession of the inferior rectus, and (3) a levator resection. Following this, the patient presented a Marcus Gunn jaw-winking phenomenon which was not noted to be present before by any of several competent observers. He does not explain the phenomenon. I have seen the movies of his patient and find it an intriguing and perplexing case.

Pagani [7] reported a case of Marcus Gunn syndrome in a 19-year-old girl. He did a levator shortening operation and states that an almost perfect result was obtained. It would seem that extreme voluntary control would be necessary in order for the result of a levator shortening to even approach perfection in this condition. I would hesitate long before doing this operation in ptosis with jaw winking.

Tumors.—As pathologists become more adept in classifying cells by smear technique, the Papanicolaou method becomes of increasing value in ophthalmology. Gaipa [8] reports a group of ophthalmologic cases in which it was used, including six cases of basal-cell carcinoma of the lid, with positive results. Biopsy is a simple procedure and should certainly be used more often than it is. But taking a smear is simpler, and perhaps surgeons and patients will not resist its use. At present, at least in lid tumors, it should not supplant biopsy.

Much has been written over many years on the merits of radiation and surgery in the treatment of eyelid tumors. The Reeh and Hyman [9] article, which was reviewed last year, is, in my opinion, the best that has appeared. Wildermuth and Evans [10] state that a lesion 5 mm. or less in diameter is best treated by excision and primary closure. If the lesion requires sacrifice of the full substance of the lid, they advise radiation therapy. A total of 4000 r in 10 treatments over about a two-week period has become the established dosage, they say.

Kreibig [11] advocates surgery where possible, because he feels that the results of radiation are uncertain. Deep foci may remain under an apparently cured skin. He believes that surgery affords proof of complete removal. He recommends a 3 mm. border beyond the visible limits of the tumor and says that if one is in doubt as to the complete removal postoperative radiation should be given.

Brown and Fryer [12] feel that excision and immediate plastic repair when possible is the treatment of choice for carcinoma of the eyelids.

The answer to the problem of treatment in these cases cannot be settled by a contribution to the literauture. Each case must be carefully considered, and a method of

treatment best suited for that case must be instituted. The patient has one golden opportunity for cure—the first attempt. Recurrences are difficult to handle. A factor which is not often mentioned is the experience and ability of the surgeon or radiologist. I believe it to be the most important factor.

Weizenblatt [13] reported on a case of a typical cyst of a Moll gland which became opaque and dimpled. Excision showed basal-cell carcinoma which did not extend beyond the cyst.

Two articles appeared in the ARCHIVES in December, 1956, which tend to clarify the confusion on ocular and dermal melanosis. Helmick and Pringle [14] suggest the term oculocutaneous melanosis to replace the more commonly used "nevus of Ota." Fitzpatrick, Zeller, Kukita, and Kitamura [15] discuss the confusion of names which are used in this benign condition which simulates malignant disease. Since the ectopic melanin-containing cells are termed melanocytes, they suggest the following changes in terminology:

Present	Proposed
Melanosis bulbi	Ocular melanocytosis
Nevus of Ota	Oculodermal melanocytosis
Mongolian spot	Dermal melanocytosis

The literature on these conditions is not large, but it is confusing. They are not seen frequently but are far from being rare. These articles are good contributions.

Last year two articles on keratocanthoma were reviewed. This is an inflammatory condition of the eyelid which is histologically indistinguishable from squamous-cell carcinoma of a low degree of malignancy. The history of growth from its start to maximum size in four to eight weeks with a spontaneous regression (should it be allowed) in four to six months is the diagnostic criterion. Last year it was stated that wide excision was advised. Crisman and Christensen [16] now state that shaving the lesion at its base and electrodesiccation of the base is the best treatment, although they do state that the lesion is radiosensitive. If spontaneous regression is allowed, a cosmetically disfiguring scar may result.

Hagar [17] also wrote on the characteristics of keratocanthoma. He feels that excision, cauterization, or small doses of x-rays are all successful in the treatment of the condition.

Metastatic carcinoma of the eyelid is rare. Ostriker [18] reported a case of this which occurred one and one-half years after removal of an adenocarcinoma of the colon. The patient was in a terminal condition, and the diagnosis was evident even before the pathologist's report. The lesion was under the upper lid and had to be removed for ocular comfort.

A rare entity, the simultaneous development of lymphosarcomatous lesions in all four eyelids, was reported by Ayberk.[19] The only treatment given was mechlorethamine (nitrogen mustard). The lesion regressed soon after the start of this treatment, and there was no evidence of recurrence in the lids or elsewhere after four years.

Entropion, Ectropion, and Lagophthalmos.—Three articles have appeared on the surgical correction of spastic entropion. Schimek's [20] operation consists of a buried nonabsorbable surgical (silk) suture attached to the orbicularis muscle anterior to the tarsus 3 or 4 mm. nasal to the center of the lower eyelid. It is brought out through an incision 2 cm. lateral to and 0.5 cm. above the lateral canthus and then fixed in the orbicularis and temporal fascia deep in this incision. It is tied tight enough to produce a slight ectropion, which, the author says, will disappear. He reported 2 recurrences in 23 cases. Schimek's discussion of entropion and his historical review of the surgical procedures which have been used is very complete. His results of less than 10% recurrences with an average follow-up of almost two years seem very good. There were two infections necessitating removal of the suture. This is somewhat similar to the complication seen in the Friedenwald-Guyton ptosis operation, and I fear that my enthusiasm would wane were I to have 10% infections. I have had

improved results since I have been using the Wies [21] operation, which was discussed last year. I do not like to change something that seems to work well and will probably await a few failures before changing to the Schimek operation.

Bodian [22] described a modification of an operation for spastic entropion popular in France. He exposes the orbicularis muscle of the lower eyelid through a skin incision. He then cauterizes the muscle rather freely with diathermy, electrodesiccation, or a heated muscle hook. He then excises a crescent of skin and closes the wound. He reports 10 cases with follow-ups of 6 to 33 months. There were no recurrences. This seems a good report for so simple a procedure, but the number of cases is small. Bodian asks that others try the procedure in order that it can be better evaluated.

Szlazak's [23] operation is a modification of the Wheeler orbicularis shortening. He shortens the muscle more along the lower border of the strip than along the upper border. He does not give any case reports or rate of recurrences.

Fox [24] reported two cases of congenital entropion occurring in siblings. This type of entropion is rare and is caused by hypertrophy of the marginal fibers of the orbicularis. This rolls the lid margin in. In contrast to epiblepharon, which usually disappears, congenital entropion requires surgery. Fox repaired it by excision of a strip of skin and muscle. Levitt [25] reported on the same condition, emphasizing, as did Fox, that epiblepharon rarely requires surgery while congenital entropion requires early surgical correction.

Barrett [26] reported a case of extreme cicatricial ectropion of the lower eyelids, the result of an inflammatory disease, probably syphiloderm. It was repaired by large full-thickness grafts taken from the inner aspects of the upper arms. Since such advanced cases are unusual and since the final result in this case was better than one would anticipate, this case report is of value.

Lagophthalmos due to facial nerve section or paralysis is distressing to the patient. Balza [27] treated five cases with a rhomboid suture similar to the Friedenwald-Guyton suture but with a white silk suture running along the margin of the lower eyelid. The results were good in three cases and inadequate in one, and in one an infection necessitated removal of the suture. This latter seems to be a complication that is inevitable in a percentage of buried sutures used in the eyelids. Velhagen [28] treated lagophthalmos by transplanting strips of the temporalis muscle to the upper and lower eyelids. He claimed satisfactory results in three out of five cases.

Inflammatory Diseases.—When one thinks of the number of routine vaccinations that are done, it seems strange that accidental vaccinia of the eyelids is so seldom seen. Taylor [29] reported a case of this and included a good discussion of the possible modes of infection. Usually the disease is self-limited, but complications such as symblepharon, corneal ulcer, and disciform keratitis may occur. In an eczematous child eczema vacinnatum may occur, with a mortality rate reported to be 33%. In severe cases treatment may include vaccinia-immune serum or vaccinia γ-globulin.

Herpes zoster ophthalmicus was successfully and dramatically relieved in one case reported by Glasser [30] by the use of antihistamines. Benedict [31] advises the use of corticosteroids in this disease. Many physicians, having heard of the activation of the herpes simplex virus by the steroids, fear to use them for herpes zoster. Many physicians, on the other hand, have not heard of the activation of herpes simplex and use no caution in the use of steroids. I think that it would be wise for the pharmaceutical houses to give equal billing to contraindications and indications when campaigning with new drugs.

Borrie [32] reported on the general field of eczema of the eyelids and divided 238 cases into (1) dermatitis medicamentosa, (2) contact dermatitis, (3) suspender der-

matitis (a nickel sensitivity), (4) infective dermatitis, (5) neurodermatitis, (6) constitutional eczema, and (7) eczema of unknown origin. Infective dermatitis was most frequent and was the most difficult to treat. Neomycin and hydrocortisone ointment seemed most effective. Dermatitis medicamentosa was the next largest group, and most of these cases were due to penicillin. Contact dermatitis was frequent, but only 10% of these cases were due to cosmetics, most of the cases being of industrial origin.

Most of us see an occasional case of phthiriasis palpebrarum, infection of the eyelid by the crab louse. Caccamise [33] reported one such case and discussed the general as well as the local treatment. He calls attention to the use of physostigmine (Eserine) ointment, as originally suggested by Cogan and Grant, for this condition.

Reconstructive Eyelid Surgery.—Total reconstruction of an upper eyelid is a difficult procedure and one which often leads to an unsatisfactory result. A new type of blepharoplasty was presented by Gandolfi.[34] He utilized buccal mucosa and a pedunculated skin flap from the frontal region in reconstructing an upper lid which had to be totally removed for a diffuse carcinoma. There are not many operations which can be used in total blepharoplasty of an upper eyelid, and this one is a welcome addition. There are good figures depicting the steps. Those who do this type of work will benefit by a study of them.

A new method for replacement of a lower eyelid was reported by Cavka.[35] A large bridge flap left attached at the two ends is fashioned just above the brow. This furnishes sufficient skin to reconstruct an entire lower lid and even part of the upper lid. It has been my experience that skin from this area is somewhat thick for eyelid skin replacement. I have used it on occasion as a single-based flap with fair results but have felt that skin from other areas might have been better.

Two articles by Singer [36,37] have appeared. One concerns basic causes of failure in grafting of skin and mucus membrane to the lids and socket. This article does not lend itself to summary. It concerns many basic considerations which are not new. Since articles dealing with failures are a rarity in medical literature, I was glad to see this one. The other article by Singer is upon the management of lid injuries. It also is a basic article and does not offer anything new. It does call attention to the Minsky type of repair for lid margin injuries. This procedure did not appear in the ophthalmic literature but in a general surgical publication [38] and was hence lost to most ophthalmologists. A few moments spent in looking up this reference would be well worth while.

Following an auto accident an infant developed a hematoma of an upper eyelid, the swelling of which persisted after the discoloration had disappeared. In this case, reported by Bagolini,[39] spinal fluid was found to be leaking into the lid from a fracture of the superior orbital plate. I have on several occasions been startled by the sudden appearance of clear fluid when operating on traumatized upper eyelid and orbital cases. Ophthalmic surgeons should be prepared to pursue this complication to its correction when they encounter it in reconstructive work. The defects of injury do not respect the arbitrary boundaries of the specialties.

Developmental Anomalies.—Three articles have appeared on ankyloblepharon during the past year. This is a rare condition which is rather easily corrected with a pair of scissors or by minor plastic procedures. Of the three references, one concerned the outer portion of the lids; one, the center, and one, the inner angle. In Smillie's [40] case external ankyloblepharon caused a pseudoptosis and a pseudoexotropia. Khanna's [41] case was of the filiform type involving the middle portions of the lids. He reasoned that a predisposing factor must have been present before the 10th week of

intrauterine life. Mielnick and Przyborowska's [42] case involved the portion of the lid slits overlying the canaliculi.

Miscellaneous.—Sayoc [43] has written considerably upon the lid folds. He states that in most Orientals with slit eyes the fold is missing because of the lack of insertion of the terminal levator fibers into the skin. The presence or absence of a lid fold is of considerable importance in ptosis surgery. We should not rule out some levator function by the absence of a fold in Orientals with slit-type eyes.

Retraction of the upper eyelid is usually caused by overstimulation of the sympathetics supplying Müller's muscle. Ottonello [44] reported four cases in which unilateral lid retraction was a sign of myasthenia gravis. He felt that this retraction was a purely muscular one caused by a compensatory hyperasthenic condition of Müller's muscle. Elander, Bedrossian, and Schaerer [45] reported a case of unilateral upper lid retraction caused by sympathetic irritation from a complete obstruction of the common carotid artery at the level of the third and fourth cervical vertebrae. It was relieved by a superior cervical ganglionectomy.

Lacrimal Apparatus

Anatomy and Physiology.—An excellent paper by Jones [46] based upon dissections of the tear sac region revises the author's concept of the "lacrimal pump." Jones has an excellent background in anatomy, and his knowledge of this region combined with his clinical experience gives considerable support to his ideas on how the tears get from the eye to the inferior meatus of the nose. His dissections have shown the lacrimal fossa to be converted into a completely closed cavity by the lacrimal diaphragm, composed of a sheath reflected from the periorbita. Alternate negative and positive pressures are created by lateral and medial movements of this diaphragm. These are, in turn, brought about by action of the superficial and deep heads of the pretarsal muscle and the deep head of the preseptal muscle. This muscular control of the diaphragm is present in both lids. The pump-like action of this mechanism serves to draw tears into the sac and express them into the nose. I am convinced that this is correct. Now, I do not understand why patients who have undergone the type of dacryocystorhinostomy which removes all but a small bit of the temporal wall of the sac do not have epiphora, at least most of them do not.

Phillips and George [47] made a radiographic study of the nasolacrimal canal. By directing the rays down from the frontal region toward a dental film held in the roof of the mouth, they developed a technique of filming the bony canal end-on. They compared a series of normal persons with a series of patients with nasolacrimal obstruction and found no difference in size between the two groups. Also, there was no difference in size between the obstructed and the unobstructed side. This led to the conclusion that bony abnormalities are of little importance as a cause of epiphora.

Hanney [48] carried on radiographic studies on the emptying of dye from the tear sac. He injected 0.5 cc. of 40% Iodipin into the tear sac and found that in 90% of 134 patients the sac was empty in 10 minutes. This is somewhat faster than the 30 minutes which Demorest and Milder [49] used as a criterion in their article, which was reviewed last year.

In a study of the protein content of tears Brunish [50] found electrophoretically that emotional tears contained appreciably more albumin than tears produced by irritation. With but little imagination one could devise practical applications for this test.

Problems in Lacrimal Obstruction.—A symposium on problems of lacrimal obstruction by Evans, MacBeth, Lyle, Summerskill, Burn, and Rycroft [51] is contained in the *Transactions of the Ophthalmologic Society of the United Kingdom* for 1956. This is an excellent review of the problem. In the opening paper Evans discusses lacrimal obstruction with reference to age groups.

He classifies them as neonatal, youthful, and over 30. The neonatal group, he feels, is largely spontaneously cured. The youthful group includes those cases due to Streptothrix infection and trauma, more in the latter group. The "over 30" group is comprised of the more commonly seen obstructive cases which require surgery. Evans brings out the predominance in females by a 4:1 ratio. In my experience, the ratio has been even higher. It is a well-known clinical observation, but I have not seen it discussed at any length before. Evans feels that the fact that women may have a smaller lumen to the bony nasolacrimal canal than men may have some influence on this. However, he states that general mucosal thickening with muscular atonia or flabbiness, all part of the "middle-aged spread," are the principal factors. There must be a better explanation. Rycroft calls attention again to subtotal lacrimal adenectomy in a small group of patients in whom epiphora persists after usual treatments. He warns that the blink reflex must be good and that there must be adequate lid coverage. The remainder of the symposium is well worth reading, although it does not contain any new developments.

Bideau and Levasseur [52] ask, "Is lacrimal intubation so bad?" They slit the upper canaliculus and pass the canaliculus knife through the nasolacrimal duct to sever any adhesions. They then introduce the tube over a stylet. They report good results in 12 of 16 patients treated over a one-year period.

Weizenblatt [53] reported a case of extensive granuloma of the tear sac resulting from a polyethylene tube which had been left in place for two years. This was a small tube and extended from the sac into the inferior meatus. Since there was no drainage through the tube, it was exposed to purulent secretions over a period of time. The author felt that this resulted in a breakdown of the tubing, resulting in the granuloma. Certainly, if tubes are to be used, they should be of a large enough caliber to permit drainage.

I expressed myself on lacrimal intubation in last year's review and have not changed my opinion. I am glad to see that LeGrand [54] has changed his. In last year's reference [55] he reported 68% success after two months. However, in one year this had dropped to 52%. He quoted Bietti as having only 20% success after three years. LeGrand now feels that lacrimal intubation should be used only rarely as a substitute for dacryocystorhinostomy.

Natchkepia and Chkoniya [56] report what they term a new nonoperative method of treatment of stenosis of the lacrimal canaliculi. In five cases they threaded a silk suture through the stenosed canaliculus and into the nose, leaving it for two to three weeks. Their follow-up was short, being only four to six weeks. Stenosis of the canaliculus has always been a difficult problem. I think that here polyethylene has a definite place. The method of Veirs [57] or some minor modification of it makes it a simple and relatively successful procedure.

Wynne Parry [58] suggests a type of skin incision for dacryocystorhinostomy different from the one ordinarily used. He makes a 1 in. (2.5 cm.) vertical incision only 2 mm. from the inner canthus. From the ends of this, two horizontal incisions are made anteriorly. The skin flap thus formed is retracted forward. He feels that the tear sac area can be more easily exposed in this way. He states that there is little if any resulting scar. In patients with long thin noses there is often a tendency for bowstring formation from the usual tear sac incision. This usually disappears after many months of time and massage, but during this time the patients are often unhappy. Wynne Parry's incision may prevent this complication. It also makes the postoperative use of spectacles less uncomfortable.

Holland [59] has written an article calling attention to Summerskill's dacryocystorhinostomy. This is an operation which appeared in the British literature in 1949 and 1952 and which Holland feels has not received due attention. An incision is made into the tear sac, which is cleaned. A trocar

is passed through the inferior medial wall of the sac into the nasal cavity. A polyethylene tube is placed in this opening. The tube fits snuggly and is apparently left in place without sutures. Somehow this scares me, as I am not a bronchoscopist.

Björk [60] discussed dacryocystorhinostomy from the aspect of the otorhinolaryngologist. He feels that preoperative examination of the nose will reveal the cause of the obstruction in about 10% to 20% of the cases, usually ozena, lupus, tumor, or trauma. He recommends the intranasal approach in most cases, and in all cases of phlegmonous dacryocystitis, deformity of the nose, and unsuccessful results after an external approach.

Vukovich [61] reported 13 of 16 cases of adults with obstructed nasolacrimal ducts successfully treated by probing followed by irrigation with naphazoline (Privine) and repeated filling of the sac and duct with a mixture of cortisone and Hirudoid ointment, whatever that may be.

Wolfson and Mariasis [62] advised forceful irrigation rather than probing in the treatment of dacryocystitis in infants. The upper canaliculus was closed with glass rod pressure. They reported, however, only 10 out of 12 successes by this method.

Braley [63] recommends probing for lacrimal obstruction in infants, preferably done before the age of 3 months. It may be done, however, up to the age of 3 or 4 years. If it is unsuccessful and purulent discharge persists after probing, he feels that a dacryocystorhinostomy should be done. For these persistent cases I have had some success with a tube placed in the nasolacrimal duct under direct view through a tear sac approach.

Lipsius [64] recommended the use of saccharin sodium in a 10% solution as an eye drop for testing patency of the lacrimal passages. It can be identified by taste in a positive test within 5 to 17 minutes. It may be of some use in children. Both sides cannot be tested on the same day, as the taste lingers. I cannot see any advantage over the fluorescein dye test, in which the disappearance of the color overlying the sclera can be used as a positive test criterion, as well as the recovery of the dye from the nose.

A new treatment for epiphora, though perhaps one of despair, is suggested by Manchester.[65] A small piece of plastic sponge is held in contact with the inner canthus by an attachment to the spectacle frame. This seems far better than a piece of tissue or a handkerchief held in contact by the fingers.

Tumors.—Tumors of the lacrimal sac, according to Jones,[66] are characterized by four stages. In Stage I epiphora is the only symptom. Stage II consists of a simulated dacryocystitis in which mucopus regurgitation results from pressure over the tear sac. Stage III occurs when a painless nonreducible swelling is present over the tear sac. Stage IV is extension of the tumor outside of the sac. There may be overlapping of these stages. The final diagnosis can be made only by biopsy, although contrast radiography may be very helpful.

Spaeth [67] feels that most tumors in the region of the lacrimal sac are primary, arising within the mucosa of the sac. In their treatment he emphasizes early diagnosis and extensive primary surgery, including removal of the prelacrimal region, the inner canthal angle of the lids, and the entire length of the bony and membranous nasolacrimal duct. Any plastic repair is delayed until one is certain that there will be no recurrence. If the tumor should recur, complete exenteration of the orbit is indicated. Radiation is useful as an adjunctive treatment. He emphasizes the high mortality and says that bold surgery is necessary.

Inflammatory Diseases.—Trachomatous involvement of the lacrimal system was considered in an extensive study by Charamis.[68] Contamination of the lacrimal gland by ascending infection is rare but does occur. Trachomatous infection in the lacrimal drainage system is common at the puncta and becomes less and less common lower in the pathway. He states that trachomatous

changes in the puncta and canaliculi are histopathologically similar to those of conjunctival trachoma. The microscopic changes resulting from trachoma of the tear sac are not distinguishable from those of dacryocystitis in general. He discusses the treatment of lacrimal trachoma, including minor surgical procedures on the canaliculi. Dacryocystorhinostomy and intubation are often tried for the relief of infection and obstruction lower down but are often unsuccessful, and dacryocystectomy may be necessary.

Milam [69] reviewed Mikulicz's disease of the lacrimal gland. He feels that there is much confusion in terminology. Mikulicz's disease should include only those painless swellings of the lacrimal, salivary, and palatine glands without loss of function and of unknown etiology. Probably more than one disease entity is involved. However, the histologic picture is characteristic and the diagnosis should not be difficult on biopsy. Accessory lacrimal gland tissue may be widely distributed in the lids and orbit, and this disease should be suspected in any lid and orbital tumor. The disease is benign and is self-limited.

Sjögren's Syndrome.—Thompson and Eadie [70] found keratoconjunctivitis sicca in 14% of 210 patients with rheumatoid arthritis. In the milder cases they recommended treatment with methylcellulose or cortisone drops. In the severer cases they advise diathermy coagulation of the lacrimal puncta. With the availability of good artificial tears, we have been using this procedure very little. However, it does afford a great amount of relief for these patients, and, if it is confined to the punctum, drainage can be reestablished if the lacrimal glands can be restored to function by hormonal or other treatment later.

Calmettes, Deodati, Planel, and Bec [71] did a valuable experimental study on the lacrimal glands of guinea pigs. They castrated 26 male and 26 female guinea pigs and examined the lacrimal glands of some of each. They found that the lacrimal glands of the males became atrophic, while those of the females became hypertrophied. In the remaining animals testosterone was given to the males and estrogen to the females. This either prevented the above changes or reversed them. While no definite conclusions are drawn, the authors suggest the importance of these findings in the pathogenesis and perhaps the treatment of Sjögren's disease.

McLenachan [72] surveyed 45 cases of Sjögren's syndrome and found evidence of liver dysfunction in the majority of these cases. He suggests that inability of the body to utilize vitamin A may explain the epithelial changes of this disease.

Rausch-Stroomann and Dörken [73] studied the steroid excretion in the urine in four patients with Sjögren's syndrome. No sign of hypofunction of the adrenal cortex was found.

Jones and Stevenson [74] reported a case of keratoconjunctivitis sicca due to sarcoidosis. They feel that this disease accounts for only a small percentage of these cases but feel that an investigation for sarcoidosis should be made. Since sarcoidosis responds to steroid therapy, permanent damage to the lacrimal gland from fibrosis can be prevented.

Developmental Anomalies.—Several case reports of congenital anomalies of the lacrimal system have appeared during the past year. Ordinarily these do not cause symptoms and require no treatment. Malhotra [75] reported a case of a 7-year-old girl who had an occlusion of the nasolacrimal duct which was treated by dacryocystorhinostomy. In addition, there was a fistula of one of the lacrimal ducts 5 mm. lateral to and 2 mm. below the lateral canthus. Tears appeared through this opening. It was necessary to transplant the duct into the conjunctival fornix to effect a cure.

Damato [76] described a similar case in a 3-month-old infant. This baby's fistula was situated in the same position as was that of Malhotra's patient. No surgery was done, although tears appeared discharging

from the orifice whenever tears flowed from the eye. Damato suggested that the fistula might be the opening of the ductule of one of the accessory lacrimal glands of Krause.

Kirk [77] reviewed congenital anomalies of the canaliculi and puncta and reported three interesting cases. These were various types of reduplication of the canaliculi and puncta. They were incidental findings, led to no symptoms, and required no treatment.

Conjunctiva

Adenovirus Infections.—On Sept. 7 and 8, 1956, a symposium on viral keratoconjunctivitis sponsored by the National Institute of Health was held in San Francisco. Taking part was a group of ophthalmologists, epidemiologists, and virologists who are attempting to clarify this aspect of virology. Included were papers on pharyngoconjunctival fever, epidemic keratoconjunctivitis, and herpetic keratoconjunctivitis and keratitis. This review is principally concerned with the first two groups. The papers presented are included in a separate (Part 2) issue of the April, 1957, *American Journal of Ophthalmology.* The majority of the papers offer nothing new, but their inclusion in one issue does make it easy for one to review the subject and bring himself reasonably up to date upon it.

Thygeson [78] opened the symposium by a general discussion of the various types of keratitis and conjunctivitis which are known to be or suspected of being of viral origin. He commented briefly on trachoma, inclusion conjunctivitis, epidemic keratoconjunctivitis, pharyngoconjunctival fever, Newcastle disease conjunctivitis, lymphogranuloma venereum keratoconjunctivitis, herpetic keratitis and keratoconjunctivitis, keratitis due to variola and vaccinia viruses, measles keratoconjunctivitis, molluscum contagiosum conjunctivitis and keratoconjunctivitis, common wart conjunctivitis and keratoconjunctivitis, mumps keratitis, herpes zoster keratitis, varicella keratitis, Beal's acute follicular conjunctivitis, chronic follicular conjunctivitis, superficial punctate keratitis, ocular pemphigus, Reiter's disease conjunctivitis, and the conjunctivitis of erythema multiforme.

Bell [79] discussed the clinical manifestations of pharyngoconjunctival fever on the basis of a study of 500 cases occurring in the Washington, D. C., area. Conjunctivitis was present in 70% of the cases.

Kimura, Hanna, Nicholas, Thygeson, and Jawetz [80] studied 27 sporadic cases of pharyngoconjunctival fever in the northern California area. An adenovirus was isolated from 13 of these cases. Eleven of these were Type 3; one was Type 2, and one was Type 6.

Ormsby, Fowle, and Doane,[81] in a group of patients in the Toronto area with eye virus infections, found Types 2, 3, 7, and 9 adenovirus, the large majority being Type 3, with Type 7 a close second. The Type 7 infections were mostly in children. They report corneal lesions in infections with Types 3 and 7.

Huebner and Rowe [82] stated that Types 3, 7', and 8 of the adenovirus group are well-established causes of ocular disease. They feel that Type 8 causes epidemic keratoconjunctivitis, rarely with any systemic symptoms.

Beale, Doane, and Ormsby [83] used human amnion cells as a culture medium in their studies. They stated that these cells may be superior to the HeLa-cell medium for study of the adenovirus.

Fowle, Simmons, and Ormsby [84] isolated four strains of Type 3 adenovirus from patients with corneal involvement. Results of cross neutralization tests indicated a close antigenic similarity of all four strains of the virus.

In discussing the epidemiology of pharyngoconjunctival fever, Bell [85] concluded that (1) infected humans were a common source of infection, (2) infection generally produced illness, (3) healthy carriers were not an important source of infection in epidemics, (4) the disease was rather highly infectious for young contacts,

(5) older persons were more likely to be immune, perhaps from previous attacks, and (6) contaminated swimming pools are a suspected but unproven source of infection. Infection and disease may be prevented, to an extent, by vaccine, but at present vaccine is not available for general use. In this regard, the Armed Forces Epidemiological Board has recommended that all recruits entering the Services by the fall of 1958 be given adenovirus inoculations routinely. The U. S. Army is currently administering them to recruits at Fort Dix, N. J.; Fort Leonard Wood, Mo., and Fort Ord, Calif.

The first paper on epidemic keratoconjunctivitis at this symposium was by Hogan,[86] who discussed the clinical characteristics of the California epidemic of 1941-1942. This was followed by Braley's [87] discussion of the New York epidemic of 1943-1946. Both authors noted similar characteristics, the percentage of cases with corneal involvement being slightly higher (92%) in the New York area as compared with California (74%).

Tanaka [88] spoke on epidemic keratoconjunctivitis in Japan and the Orient. She felt that the condition occurred in infants as well as in adults. In the infant cases there were usually systemic manifestations. Rarely did a keratitis or preauricular adenopathy occur. A pseudomembranous conjunctivitis was the usual type. In human inoculation studies she found that between 15% and 30% of persons were not susceptible.

Bietti and Bruna [89] reported on about 2500 cases seen in Italy from 1942 to 1956. Their investigation indicated that adenovirus Type 8 was the usual cause of epidemic keratoconjunctivitis in their area.

Sanders [90] was the first to isolate a virus from the early epidemic cases. It is unfortunate that definite record of his virus has been lost. However, it seems probable that the Sanders virus was not an adenovirus but was related to the St. Louis encephalitis virus. Cheever [91] carried on studies that established this relationship on two strains of virus believed to have originated from the virus pool made by Sanders in 1942.

Jawetz, Thygeson, Hanna, Nicholas, and Kimura [92] gave evidence that Type 8 adenovirus was responsible for many cases of epidemic keratoconjunctivitis but admitted that it could not be considered the sole cause.

Mitsui, Hanabusa, Minoda, and Ogata [93] inoculated Type 8 adenovirus into the eyes of five human volunteers. In three cases the results were typical. In one a conjunctivitis without keratitis developed. In one no disease resulted even after repeated trials. Serologic findings suggested a partial immunity in this patient.

Mitsui and Jawetz [94] furthered the evidence in favor of Type 8 adenovirus as the etiologic agent in epidemic keratoconjunctivitis by isolating this virus from a typical case in Japan.

Leopold [95] then discussed the characteristics of a hospital epidemic of epidemic keratoconjunctivitis, and Thygeson [96] discussed office epidemics and suggested methods of prevention.

Cockburn [97] presented a theory on the epidemiology of epidemic keratoconjunctivitis. He suggests that the causal agent is a virus of the adenovirus group whose normal habitat is the nasopharynx. When a susceptible eye is infected with this virus a relatively mild inflammation results, but should conditions exist for rapid passage of the virus through a series of susceptible eyes, then a strain is produced which is more specifically adapted to the superficial tissues of the eye, and the lesions of typical epidemic keratoconjunctivitis are produced. Cockburn presents clinical evidence in support of his theory.

Thygeson and Jawetz [98] summarized the symposium in a six-page conclusion to this special issue of the *American Journal of Opthalmology*, which crystalizes many of the points brought out. This summary is concise and is worth reading.

In a discussion of epidemic keratoconjunctivitis in Ceylon, Weerekoon [99] brought out the differences in the clinical appearance in different areas of the world. It is an occupational disease of the paddy workers in Ceylon. The corneal lesions are quite different from those seen in most areas in that they range up to 4 mm. in diameter and remain for many years if not indefinitely. Weerekoon emphasizes that epidemic keratoconjunctivitis is a blinding disease in Ceylon and states that, fortunately, if treated early with chlortetracycline (Aureomycin), oxytetracycline (Terramycin), or chloramphenicol, the disease responds well. From this description and since no virus studies were done in Weerekoon's series, one doubts that he is reporting on the disease which we term epidemic keratoconjunctivitis.

In an outbreak of keratoconjunctivitis in a home for the aged, Schneider, Kornzweig, and Feldstein [100] found treatment with oxytetracycline and chloramphenicol to be without effect. They felt that cortisone was of some value in the treatment.

An epidemic of epidemic keratoconjunctivitis in Barcelona was reported by Casanovas and Camins.[101] They noted a high sedimentation rate in many of their cases. The disease often followed slight trauma to the eyes. This, the authors felt, could well be of etiologic and industrial significance.

Returning to pharyngoconjunctival fever, Cockburn, Rowe, and Huebner [102] tested some serum which had been drawn from 11 patients and frozen during the Greeley epidemic. Ten of these sera showed a rise in the complement-fixing-antibody titer, and eight showed a rise in neutralizing antibody titer to Type 3 adenovirus. In an intrafamilial epidemic of pharyngoconjunctival fever Van Horne, Saslaw, Anderson, Flatley, and Carr [103] found that during the acute phase of the disease the group-specific complement-fixation titers and the type-specific neutralization titers to Type 3 adenovirus rose equally. Seven months later no complement-fixing antibodies could be demonstrated, while the neutralization titers remained high.

Mortelmans [104] reported a case of oculoglandular syndrome in which the diagnosis of Newcastle disease was confirmed by haemoagglutination tests. He suggests that the Parinaud syndrome be better defined into individual diseases by laboratory aid in all cases. In private practice this is not practical, but surely in clinic cases we should make better attempts to identify causal agents.

Trachoma.—As in previous years, the literature on trachoma is voluminous. This would be expected from the high incidence of this disease. The infrequency of trachoma in American ophthalmology is not indicative of progress in its world-wide control. There is still a high incidence of trachoma among certain groups in this country—particularly the American Indians. Trachoma is not a closed chapter in medical history, even in this country. There have been many interesting articles on trachoma and the study of the trachoma virus. There have been no startling developments in treatment. The trachoma virus has not, to my knowledge, been successfully cultured, although numerous workers are attempting to do this. It is becoming better understood, particularly through the use of the electron microscope.

Suzuki,[105] preparatory to work on electron microscopic studies of the trachoma virus, studied normal human conjunctiva by this method. He cut ultrathin sections of this tissue and noted mast cells, leukocytic granules, and the Golgi apparatus of nuclei to have appearances similar to trachoma inclusions. He brought out the difficulties in differentiating mitochondria and initial bodies.

Mitsui and Suzuki [106] then studied thin sections of strips of conjunctiva taken from persons with trachoma which yielded at least 50 epithelial cells with inclusions per slide. Under the electron microscope inclusion bodies were found only in the epithelial layer. Typical elementary bodies were

usually round or elliptical in shape and measured 200 to 300mμ. Initial bodies were round or oval and measured up to 800mμ. They have no doubt that the epithelial inclusion body is actually the trachoma virus colony. They discuss the life cycle of the trachoma virus and consider the possibility of a "vegetative form" in this cycle. They do not deny the development of elementary bodies by binary fission of initial bodies.

The latest work on this subject by Mitsui, Suzuki, Hanabusa, Minoda, and Ogata [107] utilized an electron microscope with a higher resolving power. They feel that with this power they are able to confirm the existance of the previously mentioned "vegetative form." They found an envelope or membrane surrounding the virus particle, the presence of which seems to indicate an older particle. Elementary bodies do not seem to be solid granules but appear to have a fine spiral or vortex structure.

In another electron microscopic study of the trachoma virus, Wilczek, Feltynowski, and Przybylkiewicz [108] found three sizes of particles; 50 to 80mμ, 150 to 300mμ, and 450 to 500mμ. They did not identify these in this paper but did feel that they were forms of the trachoma virus, as control studies of bacterial conjunctivitis cases did not show any similar particles.

In another paper Wilczek [109] expressed the opinion that the trachoma virus may have a latent stage during which it penetrates deeply into the tissues. He feels that the antibiotics act upon the virus.

Postic [110] also believes that the trachoma virus penetrates into the subepithelial tissues and that the virus itself is responsible for follicle formation.

Yuge and Kasii [111] did complement-fixation studies on the fixed trachoma virus of Arakawa and Kitamura. The test was positive with serum from 46 of 81 patients with apparent trachoma. The test showed the highest number of positives in Trachoma II. In controls with fixed inclusion blenorrhoea virus, the tests were all negative. They felt that the identification of the fixed trachoma virus with trachoma was verified by their studies.

Mori [112] attempted serial passage of trachoma virus through rabbit testicles. He found inclusion bodies in the epithelial cells of the tunica vaginalis. However, similar inclusion bodies were found after the injection of various other materials, and the author concluded that these initial bodies were caused by nonspecific inflammation and that the rabbit testicle is not suitable for cultivation of the virus of trachoma.

Thygeson and Crocker [113] wrote on the difficulties in experimental trachoma work. Experimental work on monkeys and apes has been complicated by a spontaneous folliculosis which appears in these animals. In baboons and monkeys it is possible to produce experimental inclusion blenorrhea, but the disease produced with trachoma material is mild and insidious and has little or no resemblance to human trachoma. There is never any corneal involvement or conjunctival scarring. No inclusion bodies can be found in the scrapings. Attempts to increase the severity of the disease with steroids was unsuccessful. They conclude that any conclusions based on monkey or baboon studies in trachoma must be confirmed by experiments on human volunteers.

Poleff [114] was successful in transmitting the trachoma virus to the lip. Here it produces follicles and intracellular inclusion bodies which he feels are comparable to conjunctival reactions. This is of interest in the study of trachoma immunity and virus culture. Postic [115] was unable to create what he felt was a definite trachomatous reaction in similar attempts last year.

Szeghy, Kahan, and Vajda [116-118] made studies of the tears of persons with trachoma. They found that trachoma tears have an antiheparin or a blood clotting factor, that they contain an enzyme derived from disintegrating lymphocytes which dissolves fibrin and may have a virus neutralizing effect, and that trachoma tears contain a factor which agglutinates chick erythrocytes and which is inhibited by normal tears.

Sysoev [119] states that unhealed foci containing Prowazek inclusion bodies may be found in Trachoma IV. He also feels that these bodies may be harbored by healthy persons acting as carriers. These factors have some epidemiological significance.

Carenini and Cambiaggi [120] made a slit-lamp study of aqueous veins in 116 normal and 98 Trachoma III or IV eyes. In the normal eyes 336 aqueous veins were found, while in the trachomatous eyes they were able to find only 114. They conclude that this explains the frequent complication of glaucoma in trachoma eyes. They plan further studies tonographically.

An extremely valuable experimental study on human volunteers was done by Tsutsui, Furusawa, Tsuji, and Takeda.[121] These authors, three nurses, and the wife of one of the authors submitted to repeated direct inoculations with trachoma material. After the infections were followed for varying periods, they were treated with antibiotics. When they appeared cured, reinfection was carried out by the same technique. Most of the onsets were acute—particularly the earlier infections. After the third or fourth infection the intensity became less and less severe, and finally the disease occurred only mildly. It was impossible to attain complete immunity, but relative immunity could be produced. The frequency of inclusion bodies in the scrapings diminished in proportion to the repetition of the infection. Immune serum from a person who had had repeated infections retarded the disease in another but did not prevent it.

A comprehensive article on the pathologic anatomy of trachoma by the late Prof. Yasushi Nakamura,[122] of Tokyo, appeared in the *Revue internationale du trachome.* By selective staining techniques he traces the evolution of trachoma in the conjunctival, corneal, lacrimal, and intraocular tissues. Trachomatous granulations are developed in the adenoid bed. They are made up of a germinal center of lymphoblasts and reticular cells and a peripheral zone of round cells. As the lesion advances, lymphocytes, plasmocytes, and polynuclear cells are found. The follicles eventually rupture or undergo resorption with cicatrization.

In the deep adenoid and subconjunctival layers mast cells gather in great numbers. In the precicatricial stage the lymphatic vessels of the submucosa dilate and lymphocytes, lymphoblasts, plasmocytes, and histiocytes in the stage of division are seen. Plasma cells become more prominent, and polynuclear cells diminish.

When the tarsal conjunctiva is invaded, lymphoid cells invade the fibrous tissue of the tarsus. Diffuse infiltration finally invades the musculature of the lid, resulting in ptosis.

Finally, hyaline degeneration, fatty degeneration, calcium deposits, and even ossification are seen. Colloid degeneration is sometimes seen, but only in the tarsus.

The corneal changes may be similar to those of the conjunctiva. They are discussed at length. There may be cicatrization extending into the lacrimal gland, resulting in atrophy of the gland tissue and xerosis. Nakamura states, as does Charamis,[68] that the trachomatous changes in the lacrimal drainage channels are difficult to distinguish pathologically.

Nakamura discusses electron microscopic studies, attempts at culture of the trachoma virus, and the mass treatment of trachoma in Japan. Chlortetracycline and oxytetracycline ointments have been used with success. The percentage of trachoma patients in Japan has been reduced from 24% in 1919 to 5% at present.

Kamiya [123] reported on the mass treatment for trachoma of 24,182 patients in a district of Japan. In the larger cities of Japan there is very litle trachoma, but in the villages in some areas it is seen in nearly 100% of the population. The Governor of the Nara Prefecture decided upon a four-year program to eradicate the disease. It was verified that the incidence of trachoma was largely dependent upon the living conditions. The stimuli produced by an unsanitary environment were important in allow-

ing the trachoma virus to gain a foothold. Improvement of sanitation in the villages resulted in a marked lowering of the incidence. In treating active cases chlortetracycline ointment was administered under the lower lid once daily. A few patients were treated with oxytetracycline and chloramphenicol. About 37% improved until after one month of treatment there were no inflammatory signs. Kamiya described a "pretrachoma," a conjunctivitis caused by dust, smoke, dirty water, etc., which acted as a fertile soil for the development of trachoma. He feels that the treatment of "pretrachoma" is important in the control of trachoma.

In an excellent discussion of the problems of ocular virology Bietti [124] states that the most practical treatment for trachoma is the oral administration of small to moderate doses of sulfonamides in three monthly cycles of three weeks each. In addition, local antibiotics are given.

Torfeh [125] advised the daily injection of chloramphenicol together with ointment of the same drug instilled twice daily. He noted no allergies and felt the treatment to be of unquestioned efficiency. Hasan [126] used the same medication locally and orally and noted pannus to regress in two weeks. Inclusion bodies and follicles disappeared within six weeks.

Gupta [127] used ointments of chloramphenicol and oxytetracycline and noted pannus disappearance in 12 days, with cures in 3 to 8 weeks.

Holland [128] used subconjunctival injections of 0.25 gm. of chloramphenicol given every three to six days into the upper fornix. The reactions were severe, but the results were excellent, symptoms disappearing in one to three weeks.

Oykut [129] says that a combination of oxytetracycline and polymyxin is more effective when used locally than oxytetracycline alone. He says that 80% of the acute cases and 30% to 50% of the chronic cases can be cured by this treatment. Constantinovits [130] treated 22 patients with trachoma with oxytetracycline in one eye and erythromycin in the other. He felt that the results were about equal with these two drugs.

The local use of oxytetracycline in trachoma therapy was recommended by Voinova, Zatzepina, and Musina.[131] Of 200 patients 116 were cured and 169 were improved with six daily applications. They felt that expression and massage of the follicles increased the effectiveness of the antibiotic treatment.

Proptopopov and Galchin [132] used Ethylcellusolf, a monoethyl ester of ethylene glycol, as a "conductor" to carry antibiotics into the deeper tissues. They felt that the results were better with this combination than with the antibiotics alone.

A new treatment for pannus was presented by Sinitsin.[133] In 132 patients he implanted a 15 mm. piece of absorbable surgical (gut) suture 2 to 5 mm. above the limbus. A granulomatous roll developed which diverted the blood vessels from the cornea so that they became obliterated. If the pannus is marked, he recommends an additional peritomy.

Sédan [134,135] reported on 25 years of experience in the use of tannic acid for the control of cicatricial trachoma. He uses 3% tannic acid in glycerin "endlessly repeated," there being no contraindication to its perpetual use. There is little reaction, and the long-term results are good. He took conjunctival cultures in two groups of trachoma patients, one "tanned" and one "untanned." After six months the "tanned" patients almost all had negative cultures while all of the "untanned" patients had positive cultures.

Sasaki [136] feels that perhaps some cases of apparent trachoma are not caused by the trachoma virus but represent a syndrome which appears clinically severe but shows no inclusion bodies. These cases do not respond to modern therapy. Sasaki recommends classical treatment or the use of cortisone in their treatment.

Other Inflammatory Diseases.—The effectiveness of various agents used in the

porphylaxis of ophthalmia neonatorum continues to be the subject of statistical studies. Chapman [137] compared oxytetracyline with a silver iodide preparation (Neo-Silvol), concluding that the antibiotic protected the eyes from pathogens as well as or better than the silver preparation. Siebeck and Walch [138] tried a quaternary ammonium antiseptic in prophylaxis. They had used a substance called Quartamon in preparing eyes for a total of 1875 intraocular operations with success. They found it to have a wide spectrum and to be stable and free from many of the disadvantages of the antibiotics. They found concentrations of 0.05% to be 100% effective against gonococci. Concentrations up to 0.5% were nonirritating to rabbit conjunctivae. They found that when used in the eyes of newborn infants it was more effective than silver nitrate and caused fewer conjunctival reactions.

Von Zahn [139] used a substance called Didrosulfon, which is a combination of Aristamid and dihydrostreptomycin, in the treatment of bacterial keratitis and conjunctivitis. He found it to be effective against staphylococci, pneumococci, diplobacilli, and streptococci. In four patients with herpetic keratitis he reported encouraging results.

Tomila and Forsius [140] studied the bacteria found in 60 cases of conjunctivitis and dacryocystitis. They emphasized that it is impossible to determine the effective antibiotic from the type of organism and that sensitivity tests are indispensable as a therapeutic guide.

Norn [141] made conjunctival cytologic studies on 305 patients with various types of conjunctivitis. Since the findings were not particularly helpful clinically, he concluded that the primary clinical diagnosis was more correct than was the cytological diagnosis. He did feel that cytological studies were of some value in uncertain cases or where treatment had been unsuccessful.

Herm [142] reported a case of severe membranous conjunctivitis caused by β-hemolytic streptococci. It was treated with penicillin, sulfisoxazole (Gantrisin), bacitracin, streptokinase-streptodornase, typhoid vaccine, and cortisone. In spite of the fact that the outer third of the corneal stroma became infiltrated and sloughed, it reepithelialized, with a resulting vision of 20/40. Such cases are rare. Such recoveries are rarer.

Bobrova [143] wrote on the treatment of tuberculosis of the conjunctiva. He feels that the infection is hematogenous. He recommends streptomycin given both subconjunctivally and by iontophoresis. From 10 to 40 injections of 50,000 units are given. Regression requires 6 to 16 weeks. In the five cases treated there were no recurrences.

Crick [144] studied 63 patients with clinical evidence of sarcoidosis in areas other than the eyes. He found that approximately one-fourth of them had sarcoid lesions in the conjunctiva. Typical follicles were found in the loose folds of the lower fornix. They are large and often confluent. They are translucent and have an orange tinge. Biopsy of these is simple and is of diagnostic value.

Lippmann [145] drew attention to the local irritating effect of steroid suspensions used as eye drops and in ointment form. Reports on the effectiveness of the recently introduced steroid solutions are awaited by many who have noted these irritating effects. Lippmann states that clinical effectiveness and tissue penetration are not parallel in the use of steroids locally. If the agent penetrates too fast, it may be ineffective for surface lesions.

Tumors.—A 1955 article by Greer [146] was overlooked last year and should be included in this review. This author is an authority on pigmented lesions of the eye. The present article is, in my opinion, an outstanding contribution to the clarification of pigmented tumors of the conjunctiva. Pigmented tumors are divided into three groups: benign, precancerous, and malignant. The benign group includes the deep nevus, the junctional and compound nevi, juvenile melanoma, and blue nevus. The precancerous

group includes lentigo malignum, activated junctional nevus, and precancerous melanosis. The malignant group includes the malignant melanoma or melanocarcinoma and the malignant blue nevus.

The nevus cells in the deep nevus occur only in the submucosa. They are deeply pigmented. The overlying epithelium is intact, and there is no proliferation of the junctional cells. This type rarely if ever becomes malignant.

The junctional nevus forms at the junction of epithelium and submucosa. Proliferating clusters of melanoblasts in the basal layers of the epithelium are the distinguishing feature. The nevus cells have a tendency to drop down into the superficial submucosa. This is a benign phase. However, the overlying epithelium may be in a state of unrest, and this may result in malignant change. A most constant sign of activity is the migration of proliferating cells upward, toward the surface. Actual malignancy occurs when the proliferated cells in the junctional layer actively invade the submucosa. According to Greer, the pathologist must ask two questions: 1. Are the proliferating cells anaplastic? 2. Do they penetrate the submucosa? If the answer to both is "yes," the lesion is melanocarcinoma. If the answer to one is "yes," the lesion is precancerous and does not require such radical treatment.

Juvenile melanoma is histologically malignant but is usually clinically benign. Greer believes that most melanocarcinomas arise from a preexisting pigmented nevus. This varies from the teachings of Reese, who believes that they arise from precancerous melanosis. Blue nevus is rare in the conjunctiva and only very rarely becomes malignant.

Greer,[147] in another paper, says that the intraepithelial proliferation in the basal layers of the epithelium in precancerous melanosis is analogous to Bowen's intraepithelial carcinoma.

Dimolt and McAdams[148] reported upon the attempted use of the Papanicolaou stain to support the diagnosis in a case of intraepithelial carcinoma of the limbus. It was not diagnostic but was reported as suspicious of malignancy.

Trevor-Roper[149] reported six cases of intraepithelial epithelioma of the conjunctiva, one of which involved the tarsal conjunctiva, a rare site for this lesion. Because of its remoteness from the eye, this one was treated successfully by β-radiation. The author states that he believes surgical excision to be the simplest and surest method of treatment.

François, Rabaey, and Evans[150] classified epithelial tumors of the conjunctiva into (1) epithelial hyperplasia, (2) hyperplasia papillomatosa (benign and malignant), (3) intraepithelial epithelioma, and (4) epithelioma spino and baso cellularis. They advise either excision or fractionated contact radiation of 5000 to 6000 r.

Sacks[151] reported a case of a cherry-red tumor arising in the conjunctiva of the lower fornix. Histologic study revealed it to be a Kaposi tumor.

O'Rourke and O'Connor[152] reported a fatal case of lymphatic leukemia in a 15-month-old boy in which the presenting symptom was a marked injection and swelling of the lower conjunctivae.

Guimaraes[153] reviewed the characteristics of demoid tumors, lipomata, and subconjunctival dermolipomata. In the removal of these tumors he recommends the interposition of Tenon's capsule between the sclera and conjunctiva.

Pterygium.—Paiva,[154] in a paper on plastic surgery of the conjunctiva, states that 20% to 30% of pterygia will recur regardless of the method of treatment. I wish that my recurrences were only 30%. Paiva's paper reviews the various replacements for conjunctiva, pointing out their advantages and disadvantages.

Gibson[155] found a pterygium recurrence rate of 20% to 30%, which he found could be reduced to 10% by postoperative contact radiation. He recommened 2000 r in four doses over a 10-day period. He states that

(1) the younger the patient the higher the recurrence rate; (2) a "thick fleshy" pterygium is apt to recur, especially in a patient with a sandy complexion; (3) recurrence is likely if an appreciable amount of conjunctival tissue is left on the cornea at the limbus; (4) a pterygium with a tendency to recur is discouraged by the presence of a well-marked arcus senilis or a well-developed pigment cap at the edge of the pterygium, and (5) keloid tendency elsewhere on the body predisposes to pterygium recurrence.

Mead [156] feels that β-radiation postoperatively is the best treatment for pterygium. He advises 2400 r in a single dose, fractionation being unnecessary. With this dose about 480 r is delivered to the nearest part of the lens. This is safely below the 800 r which, he says, will sometimes produce lens opacities. He gives it within a few hours after the surgery.

The use of a plasma-thrombin "glue" in causing adherence of the conjunctival flap to the sclera in the surgery of pterygium is recommened by Wagner.[157] He feels that this has a favorable effect in the prevention of recurrence. Often, though, there is insufficient adhesion of the plasma-thrombin mixture.

Pinkerton [158] suggests that an important factor in the formation of pterygium is the blepharospasm caused by intense glare, wind, etc. This, he feels, causes a passive congestion of the subconjunctival tissue which is a major factor in pterygium development.

Symblepharon.—There have been a few articles in the foreign literature on the prevention of symblepharon. Zurabov [159] positions a folded piece of waxed paper in the fornix, held in place with mattress sutures. He says that it does not irritate the cornea. Chazarof [160] uses a piece of rubber from a surgical glove in a similar fashion, leaving it in place for only about one week. Bernardczykowa[161] advocates the use of acetylcholine locally in eye burns. He treats these eyes with frequent instillations of 5% solution or 2% ointment and states that vascularization of burned conjunctiva is hastened, necrotic tissue sloughs, and symblepharon formation is greatly reduced. He also feels that corneal vascularization is reduced. Surgery for symblepharon was unnecessary in cases treated by this method.

Cavka [162] reported an operation for total symblepharon similar to that of Pagani,[163] which was reviewed last year. He used a corneoscleroconjunctival graft from a cadaver sutured in place after the separation of adhesions. A conformer was used to maintain the fornices. A rather violent local reaction resulted but subsided slowly. The use of cadaver donor material in conjunctival surgery has been infrequent but opens the way for many improvements in present techniques. It is hoped that others will use it and report their results.

Anatomy.—A study of the lymphatics of the bulbar conjunctiva was made by Sugar, Riazi, and Schaffner.[164] This has been a neglected field in ophthalmic literature. A ring of collector channels was found to lead from the perilimbal vessels toward the external canthus. The largest branch found was the inferior temporal. This branch anastomoses with the lymphatics of the lids and drains into the preauricular, upper parotid, and submaxillary glands. The authors discussed lymphangiectasia of the conjunctiva, which is frequently seen and which is often annoying to the patient. They advise simple excision of these lesions.

Meighan[165] reported on a slit-lamp study of the conjunctival circulation. He noted the frequency of communicating vessels which were larger than capillaries between the arterioles and the venules. No direct arteriovenous anastomoses were seen.

Vernal Catarrh.—In an article on allergic diseases of the the external eye, Stauffer [166] stated that the best theory on the cause of vernal catarrh is that it is a conjunctival manifestation of allergy, the irritating agent being dust aggravated by dry heat—the syndrome occurring in a vagotonic person. According to Stauffer, the best therapeutic results are obtained by immuni-

zation to dust and molds and by endocrine therapy.

In discussing radiotherapy for nonmalignant diseases of the eye, Lederman [167] warned against the dangers of β-radiation for the eradication of the papules of vernal catarrh. He feels that small doses of x-radiation given one month before the expected onset of the seasonal attack are safe and will prevent or lessen the severity of the attack. His views on the safety of x-radiation in vernal catarrh are not shared by most ophthalmologists.

Gurin [168] reported the presence of inclusion bodies in conjunctival scrapings of patients with vernal catarrh. They dye violet with methylene blue. He feels that they may be coexistent and are probably caused by some virus.

In a statistical study of 666 patients with vernal catarrh, Oguchi, Kawase, Yoshinaga, Migita, and Nemoto [169] found the condition to be twice as prevalent in males as in females. The usual onset was between 11 and 20 years of age. Familial occurrences were frequent. They felt that pollens were a causative factor, as the onset was usually during the period of pollen abundance.

Guerrero-Pérez [170] considers vernal catarrh to be a general allergic process with conjunctival manifestations. He recommends oral cortisone in the treatment in doses up to 80 mg. daily for the palpebral form and local cortisone in the conjunctival form. He combines this treatment with vitamins and calcium.

Barrada [171] reported that 70% of 350 patients obtained relief of symptoms in the treatment of vernal conjunctivitis with three daily instillations of a 0.25% lactic acid solution into the conjunctival sac. This tended to neutralize the alkaline secretions, and the low-grade irritation which was produced caused fibrosis of the conjunctiva and disappearance of the papillae.

One cannot help but be impressed by the large amount that has been written compared with the small amount that is known about this common disease entity.

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News and Comment

ANNOUNCEMENTS

Special Travel Fund for International Congress.—The National Institute of Neurological Diseases and Blindness today announced the establishment of a special travel fund designed to aid younger ophthalmologists and other scientists engaged in ophthalmological teaching or research to attend the 18th International Ophthalmology Congress. The Congress is being held in Brussels, Belgium, Sept. 8-12, 1958.

The fund was made possible by a grant from the National Advisory Neurological Diseases and Blindness Council to a Council subcommittee. In authorizing the grant, the Council noted that "an International Congress offers enormous value in the training and exchange of ideas" among scientific investigators.

The subcommittee has asked that all applications for aid from the fund be made in letter form and addressed to Dr. Gordon H. Seger, Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda, Md. The letter of application should also provide a brief review of the applicant's educational and occupational background and should indicate his major field of interest.

The deadline for receipt of applications is March 1, 1958. The Council subcommittee will make its selections and notify those to be aided by letter no later than April 1, 1958. For additional information, call Mr. Edward M. Glick, Ol. 6-4000, ext. 2207.

Correspondence

ENCEPHALOMA OF THE EYE

To the Editor:—I am submitting to you for republication part of a lecture No. 8 by John Simon (General Pathology, as Conducive to the Establishment of Rational Principles for the Diagnosis and Treatment of Disease: A Course of Lectures Delivered at St. Thomas's Hospital During the Summer Session of 1850, London, 1850, p. 104). The title is "Encephaloma of the Eye," which I believe you will find not only a very vivid description but also an accurate one. I ran across this purely by accident, and it is my hope that this may stimulate an interest in some of the old medical literature.

JULIAN F. CHISHOLM JR., M.D.
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"Taking, then, out of innumerable instances that which, to my mind, seems most characteristic and typical, I would sketch you an illustration of cancer thus: A child is brought to me, blind of one eye. The loss of sight has been discovered accidentally, for there has been no complaint of pain. The pupil is largely dilated, but (with this exception) at first the eye looks healthy; the iris having its natural colour, the cornea its natural clearness and polish, the globe its natural mobility. On looking carefully, however, through the large dark pupil into the depths of the eye, I observe there (as the patient's head moves) an unusual reflection of light, as though from a small metallic mirror set in the retina. A month elapses, and I see the child again: the aspect of the large dark pupil is now altered by something white or yellowish, which seems to stand close behind it, rising from the bottom of the globe—something solid, smooth, rounded, reflective, with a red vessel or two branching on its surface. Another interval of longer duration, and I find what can no longer be overlooked, even by the non-professional observer: that pale, growing mass has advanced into the anterior chamber; the lens has become opaque and is thrust aside, or merged in the tumour; the globe is no longer healthy in appearance, but is enlarged in its transverse diameters, and seems to bulge unevenly at one or two points of its circumference; evidently it is distended, and its distension causes pain and irritation; the vessels of the conjunctiva are gorged with blood. A few weeks more—the cornea has sloughed before the augmented pressure of the tumour; the latter has burst from its confinement, and though still girt about its base by the ring of sclerotic, it expands beyond this isthmus with redoubled luxuriance, into a mushroom shape, with broad, bloody, discharging surface. Now every day tells: the sclerotic ceases to constrain the expansion of its base, which no longer seems to emanate from the globe merely, but from the whole cavity of the orbit; while its outward growth has thrust the eyelids wide asunder, and projects already far beyond their level; its discharge is immense; lumps slough from its surface; blood bursts from its vessels; a material like pus pours from it incessantly; but in spite of all this loss of substance it grows on, bigger and bigger; the wretched child meanwhile getting thinner and more hectic, as though its whole organic subsistence were gradually prolapsing through the orbit. The surrounding integuments have taken on the same fungoid activity: where they correspond to the base of the tumour, they no longer seem to confine, but rather to contribute to, its growth; blending their large pulpy vegetations with its broadened circumference. One marvels whence can be derived its flood of albuminous secretion; one hopes it may exhaust itself, and cease like the flux of an abscess; but such hope is vain: the duration of life and the circulation of blood are the only limits of its continuance.

"A little while longer gives the opportunity of post-mortem examination. The orbit is tightly occupied with what may still be called the base of the tumor—so tightly, that, if the case have lasted long, the bony walls of the cavity will have begun to undergo absorption. A section of the tumour shows a substance like brain, white, soft, and uniform, which admits of being cut in thin slices, but may easily be rubbed to a cream. It is marked with red points, indicating the section of blood vessels, and in parts is pinkish over the surface, from diffused vascularity. It is intersected and supported by a very delicate network of fibrous tissue; from the interstices of which there may be squeezed or washed out the softer pulpy elements of its structure; leaving only that slight alveolar web, as its skelton, behind. Microscopical examination shows that this mass consists substantially of nucleated cells, presenting some varieties of form, and some gradations of development, to which I shall directly give closer attention.

"On opening the cranium, it is found that the same morbid change has prolonged itself thither: the optic nerve immediately within its foramen enlarges into a lobulated mass of material, like that of the exterior disease, which extends as far as the thalamus, becoming larger behind the commissure of the optic nerves, and indenting the adjacent surfaces of brain, which are in a softened and diffluent condition from the effects of pressure.

"This picture of encephaloid cancer, as it affects the globe of the eye, is one that many of you can verify out of your own recollection; and all of you no doubt can remember some case where the family-likeness of cancer showed itself in one part of the body or another;—some case, in which a solid tumour has made its way through the skin, has continued to grow and shed its particles outwardly, has shot its roots further inward, has infected all parts around with its peculiar method of growth, and finally (supposing it to have resided in no vital organ) has destroyed the patient by sheer exhaustion and flux."

SYMBOLS FOR EXPRESSING INTRAOCULAR DYNAMICS

To the Editor:—In the past few years the treatment of intraocular dynamics in mathematical terms has become increasingly popular. Unfortunately, though there is little disagreement as to the form the equations should take, the tendency has been for a different set of symbols to be brought into use in each laboratory. This was not too serious when the exchange of substances between the blood and aqueous humor alone was being considered. Now, however, the exchanges between all the tissues and fluids of the eye are being formulated in terms of a dozen or more constants, and much unnecessary confusion would be avoided if a uniform and logical system of symbols were employed.

Accordingly, we developed a system which we circulated to those workers we knew to be active in the field. Apart from some criticism of detail it found a ready acceptance. The scheme has been modified to take account of these criticisms, and it now has the following form, which we hope will be generally useful.

Each tissue or fluid is represented by a letter in subscript: *a*, anterior aqueous humor; *h*, posterior aqueous humor (hind humor, *Hinterkammer*); *v*, vitreous humor; *c*, cornea; *l*, lens; *i*, iris; *z*, ciliary body (*Ziliarkorper*); *p*, plasma; *d*, tears (*Dacryon*).

Their volumes and masses are to be represented by V and M. Thus: V_a, M_i (volume of anterior aqueous humor, mass of iris).

The interfacial areas between them, by A. Thus: A_{ac} (area of posterior corneal surface).

The mass of a substance in a tissue or fluid, by m. Thus: m_c (mass of substance in cornea) and m_{ac}, m_{ca} (net mass moved from aqueous humor to cornea, and vice versa).

The concentration of a substance in a tissue is expressed as mass of substance per unit mass tissue by C, and is expressed as mass of substance per volume tissue water by c. Thus: C_z, c_z (mass per gram ciliary body or per milliliter ciliary body water.)

Permeability constants of membranes, by K. Thus: K_{cd} (permeability constant of corneal epithelium in direction stroma to tears).

These permeability constants are defined by the equation

$$\frac{dm_{cd}}{dt}=(K_{cd}\,C_c-K_{dc}\,C_d)\,A_{cd}$$

where t is the time.

Transfer coefficients between tissues or fluids, by k. Thus: k_{hv} (transfer coefficient from posterior chamber to vitreous). They are defined by the equation

$$\frac{dC_h}{dt}=k_{vh}\,C_v-k_{hv}\,C_h$$

Since the value of the coefficient depends on the volume of the tissue or fluid in which the concentration changes are being considered, this can be shown where there is a possibility of ambiguity by a further subscript. Thus: $k_{h.vh}$ in the equation above. Then

$$k_{v.vh}=\frac{V_h}{V_v}k_{h.vh}$$

When the transfer coefficient from a tissue or fluid into several others is to be identified, addition signs may be used. For example, the transfer coefficient from the posterior chamber into the vitreous and lens may be written $k_{h.h}$ $(v+1)$.

The total transfer coefficient out of a tissue or fluid may be written simply. Thus: k_h.

In the case of the aqueous humor, k_o, k_d, and k_f may be retained for the total transfer coefficient out, and its diffusional and flow components.

The steady-state-concentration ratio between two tissues or fluids, R. Thus: R_{ap} (ratio of concentration in aqueous humor to that in plasma).

This system can be extended to other branches of ophthalmological research where it is necessary to give symbols to the properties of the tissue or to the relationships between them.

STEWART DUKE-ELDER
DAVID M. MAURICE
Institute of Ophthalmology, University of London

OCULAR MANIFESTATIONS OF RILEY-DAY SYNDROME: FAMILIAL AUTONOMIC DYSFUNCTION

To the Editor:—The article by Liebman on ocular manifestations of Riley-Day syndrome in the November, 1956, issue of the ARCHIVES, page 719, presents descriptions and illustrations of a condition we see much of in India. The condition is the lack of vitamin A, which leads to more blindness among children in the parts of India in which I have worked than any other condition.

The dryness of the conjunctival sac, the lack of tears, is only part of a process in which the mucous membranes of the whole body loose their mucous quality and become squamous. The cornea may be dull, epithelium-thick or deeper, or may become like white blotting paper in appearance and consistency. The mystery of keratomalacia is the tremendously toxic action on the cornea. How can such a strong and beautiful organ, through which only Greishaber's needles will go easily, become so soft so quickly?

Would that Dr. Cogan, pathologist, could have obtained in the fatal case described sections of the intestine and of the lacrymal gland that was not functioning. Dr. Cogan's statement that "no goblet cells are seen in the conjunctiva, but this may not be abnormal" must be wrong. "No goblet cells" in the conjunctiva is, I am sure, of tremendous importance clinically and cannot under any circumstances be anything but abnormal.

It is interesting that in vitamin A deficiency one eye may develop keratomalacia in the center which then extends out while the other eye may have just a deepening degeneration of the cornea following on an exposure keratitis, which is in itself a malnutrition of the cornea from lack of the moisture from winking, accentuated by lack of tears themselves, the seriousness of the condition accentuated greatly by vitamin A deficiency.

In some debilitating conditions of infants and children and also in adults the eyes do not close, and in conditions where the eyes do close and perhaps are not opened, the patient keeping the lids even tightly closed, vitamin A deficiency must be anticipated and protective injections given. The continuation of a diarrhea is of very great importance, for the changes in the epithelium of the intestinal tract prevent the absorption of vitamin A, making a vicious cycle.

I have heard from ophthalmologists in America that they have not seen a patient with vitamin A deficiency in all of their lives. Such an article as Liebman's, where outstanding illustrations of vitamin A deficiency have apparently been mistaken for ocular symptoms of Riley-Day syndrome, demonstrates the need for Western oculists and pediatricians to alert themselves to the possibilities of vitamin A deficiency, chronic and acute.

Has the condition described by Liebman something to do with Riley-Day familial dysautonomia, or is it the result of a frank malnutrition headed off by vitamin A deficiency?

What was the diet of the children at home and at the hospital? Was vitamin A therapy tried out either at home or in the hospital? Was there involvement of the skin?

In these conditions where there might possibly be a vitamin A deficiency it is very necessary not to take any chances. It is most necessary to give 100,000 units of vitamin A intramuscularly, daily, in severe debilitating conditions, especially if there is any suggestion of ocular symptoms of dryness, or lack-luster, of conjunctiva or cornea. It would be tragic to follow Dr. Liebman's suggestion in such conditions and give a "protective ointment, instilled at night," some test for vitamin A deficiency being positive or negative, as the case may be.

One of the most satisfying and startling responses of the body to treatment in all of medicine is the response of the fish-scale or finger-nail appearing cornea of prekeratomalacia to an injection of vitamin A. Within fourteen hours, if caught at the right time, the cornea has regained its natural shine and clearness, to fill the surgeon with awe and gladness at the transformation. Much more vitamin A must be given over sometimes a long time, together with the establishment of an adequate diet that is absorbed, but the initial response is most gratifying. Let us not let our little, or larger, patients ever get so low in such an important ingredient of living cells.

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METRIC SYSTEM

To the Editor:—Our use among ophthalmologists in the U. S. A. of the 20/20 and other foot designations of vision and other measurements could with great profit be changed to the metric system.

For one used to the metric system, to run on to the foot designations by men of caliber in ophthalmolic science publishing articles in our American ophthalmic publications, which go around the world, and in ophthalmic publications of other countries seems to one using the metric system all of the time something unintelligible. It takes a good deal of calculation that is troublesome for one used to the metric system to translate the unscientific 20/180 and other foot figures into something understandable.

I have heard the reaction of astonishment and perplexity among those who are used to the metric system when they see us using the foot designation.

With the exception of America, the metric system is exclusively used in ophthalmology. If the U. S. A. ophthalmologists think that the foot designations are sacred, well and good, but now that the World Ophthalmological Congress is to be held next September in Brussels, may I request those sending papers to the Congress and speaking at the Congress to practice the use of the metric system throughout so as to extend the influence of American ophthalmology by the intelligent communication possible through the medium of the almost universally used metric system.

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RETINITIS PIGMENTOSA WITH NORMAL ELECTRORETINOGRAM

To the Editor:—If electroretinography has any place in clinical ophthalmology at all, then this place is surely in the differential diagnosis of the tapetoretinal degenerations. The knowledge in this field has recently been splendidly summarized by Franceschetti and Dieterle (Elektroretinographie, in Hamburg Symposium, *Bibl. Ophth.*, Fasc. 48, Basel and New York, S. Karger, 1957). In this article it is made clear by many personal contributions of the authors that an extinguished electroretinogram is not only pathognomonic for chorioretinal abiotrophies but essential in establishing the correct diagnosis in difficult or doubtful cases.

In view of this situation, it would be very significant if it could be shown that there are well-substantiated cases of retinitis pigmentosa in which there is an electroretinogram of normal shape, though possibly of reduced amplitude. Unfortunately, the case presented by Skeehan, Passmore, and Armington (A. M. A. ARCH. OPHTH. 57:536 [April] 1957) is not a well-substantiated case, or at least the information offered in this paper is too scanty to give convincing evidence that the patient actually had retinitis pigmentosa. To be sure, the patient had a ring scotoma, and some of the fundus findings (the appearance of disc and vessels) were certainly suggestive, although the clumpy pigment was much less so. But ring scotomas are not alone decisive in the diagnosis of retinitis pigmentosa, and there are certain questions that come to one's mind in studying the paper by Drs. Skeehan, Passmore, and Armington. The patient is a Negro, and among Negroes retinitis pigmentosa is a rarity; nothing is said about the behavior of his dark adaptation; the serologic status of the patient is not reported; nothing is said about possible measles and other viral infections, which, as is well known, may result in the production of a clinical picture which it is often difficult to differentiate from true retinitis pigmentosa.

It is impossible to decide with certainty from the report at hand whether the patient did or did not have retinitis pigmentosa. However, I should consider the electroretinographic evidence to be overwhelmingly against it, judging from the reports in the literature and the experience gathered in my own laboratory. It is unlikely on theoretical, pathologic, and clinical grounds that a patient with retinitis pigmentosa should have a normal electroretinogram. If I found one, I should want to make very sure that the patient does not have a so-called secondary, or pseudo, retinitis pigmentosa, such as is seen in syphilis or following a virus infection. In any event, the case presented by Drs. Skeehan, Passmore, and Armington does not call into question the differential diagnostic value of electroretinography in tapetoretinal degenerations.

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To the Editor:—The patient reported in the article was examined by numerous ophthalmologists, including the consultants to the Walter Reed Ophthalmology Service from the Wilmer Institute and from Washington, D. C. All agreed that

this was a typical case of clinical retinitis pigmentosa. The photographs do not reproduce well the "bone corpuscle" distribution of pigment which was found in this patient. The differential diagnosis of syphilis and viral infections were considered. The patient's serology was negative; there was no history of severe measles or of any other illness; the family history is certainly suggestive of a hereditary degeneration. Unfortunately, none of the patient's family have been available for study. Dark adaptation was not tested. Retinitis pigmentosa was diagnosed in one other Negro male of a total of 26 cases admitted as inpatients to Walter Reed Army Hospital from January, 1951, through September, 1956. The senior authors take responsibility for the title of the published report and some of the interpretations not concurred with by Dr. Armington. In this respect, we agree with Dr. Burian's implication that the electroretinogram should not have been defined as "normal" in the title. Although the response was similar to that of the normal eye in the light-adapted state, its subnormality became increasingly evident with the progress of dark adaptation. The electroretinogram scarcely achieved 150μv. after 30 minutes of darkness. Small as well as extinguished electroretinograms have been previously reported in retinitis pigmentosa. The interest in this case lies in the relatively larger, though still subnormal, electroretinogram that was found. The exact value of the electroretinogram as a diagnostic instrument awaits the accumulation of a much larger body of evidence than is currently at hand.

R. A. SKEEHAN JR., M.D.
J. W. PASSMORE, M.D.
JOHN C. ARMINGTON, Ph.D.
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MYDRIATIC TREATMENT OF SHALLOW CHAMBER AFTER CATARACT EXTRACTION

To the Editor:—The recent article by John Weisel and Kenneth C. Swan (A. M. A. ARCH. OPHTH. 58:126-129 [July] 1957) is very interesting and deals with a difficult problem.

I am in complete agreement with them in that delayed restoration of the anterior chamber is a different entity from late emptying of the chamber.

Much confusion has arisen through statistics referring to flat chambers that do not separate these two types.

As demonstrated by Weisel and Swan, delayed re-formation of the chamber is due to a leaking wound. They seem to have completely eliminated this type of flat chamber by their method of suturing the wound with gut sutures which are covered by a limbus-based flap.

In patients with late emptying of the chamber, on the other hand, they usually found no evidence of a leaking wound. My previous observations (A. M. A. ARCH. OPHTH. 52:250, 1954) are similar in this respect.

It seems obvious to me that tardy flattenings of the chamber must be explained, in most cases, by another mechanism than leakage. In fact, in penetrating keratoplasty, where there is a large wound connected with the anterior chamber and several stitches that could act as wicks, late emptying of the chamber is not a common complication. Besides, in filtering operations for glaucoma, which are the best examples of a leaking wound, one usually sees delayed restoration but not late emptying of the chamber.

Late emptying of the anterior chamber is an exclusive postoperative complication of lens extraction. It is therefore logical to think that it must be related to the new anatomical characteristics of the aphakic eye, as is the fact that by disappearance of the zonule-lens diaphragm the vitreous face is now in direct contact with the back of the iris and aqueous.

Could the pressure of the vitreous body on the back of the iris push it forward until it touches the cornea while the aqueous is expelled through its normal

channels? This is the theory I favor in my paper (A. M. A. ARCH. OPHTH. 52: 250, 1954) on the role of internal hernias of the vitreous as a cause of late emptying of the chamber.

Weisel and Swan are in favor of a pupillary block mechanism in their article. It seems to me difficult to reconcile the fact that they have registered hypotony as a constant finding in their patients with a mechanism of pupillary block, which should have given glaucoma.

The role of choroidal detachment is another important point. Weisel and Swan found a choroidal detachment in 10 of the 14 eyes with late emptying of the chamber. Choroidal detachment also occurred in 17 eyes with deep chambers, but with hypotony. They suggest that choroidal detachment is primarily associated with hypotony.

In my paper Case 2 was kept with a mydriatic pupil by persistent application of atropine in the postoperative period and the chamber was lost on the 11th day. No leakage of the wound could be found with the biomicroscope by the use of fluorescein. Choroidal detachment was searched for in the dark chamber, but the fundus reflex was entirely normal (mydriatic pupil). Only three days later a detachment of the choroid appeared in the superior temporal quadrant. From this case I concluded that choroidal detachment was not the cause of the flattening of the chamber, as it followed it only three days later.

Some time ago I had an experience similar to the one of Reese (Reese, A. B.: Herniation of the Anterior Hyaloid Membrane Following Uncomplicated Intracapsular Cataract Extraction, *Tr. Am. Ophth. Soc.* 46:73, 1948) following a round-pupil intracapsular extraction. A flat chamber (of late appearance) was re-formed in one and a half hours after instillation of a single drop of DFP (isoflurophate).

Diamox (acetazolamide) has helped in other cases, and when it was used the hyaloid, which was convex and taut, was seen to slacken and recede backward. An antiedematous action of Diamox on the anterior portion of the vitreous body might be postulated. One can imagine that the vitreous might absorb aqueous after the disappearance of the zonule-lens diaphragm.

There is much that is unknown about the mechanism of late emptying of the anterior chamber after cataract operations, and research on this subject is greatly needed. I sincerely hope that Drs. Weisel and Swan go ahead with their interesting investigations in this field.

ALFREDO VILLASECA, M.D.
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To the Editor:—Thank you for forwarding the comments of Dr. Alfredo Villaseca on the recent article prepared by Dr. John Weisel and me. We read his paper published in 1954 and are pleased to know that Dr. Villaseca still feels that delayed restoration of the anterior chamber due to a leaking wound is a different entity from the decreased volume in the anterior chamber which commonly occurs a week or more after surgery.

At a recent meeting of the Oregon Ophthalmological Alumni Association Dr. R. C. Cowger and I presented additional data to substantiate this view. In a series of 550 consecutive cataract extractions performed by our resident staff and faculty, the incision in the limbic stroma was closed with mild chromic gut sutures buried under a limbus-based flap. In all of these cases the anterior chamber re-formed within 24 hours, but filtration blebs of the type observed after glaucoma surgery became evident one week or more after surgery in 1.6% of these cases. These data suggest that with use of a flap and buried sutures the relatively innocuous complication of a filtration bleb formation replaces the potentially more serious complication of delayed formation of the anterior chamber due to a leaking wound. It is evident that, in the group of patients developing filtrations, aqueous was leaking into the subconjunctival tissue from the anterior chamber through a gap in the incision; however, these eyes did not have greater incidence

of shallow anterior chamber or choroidal detachment as compared with the other patients in this series of 550 operations. Our study of filtrations following cataract surgery is being prepared for publication and will be submitted to the ARCHIVES.

Dr. Villaseca has questioned whether a pupillary block can occur in presence of hypotony. It is our present belief that it can occur if there is a marked suppression of aqueous formation. For example, a marked iris bombé formation occasionally is seen without glaucoma in the late stages of severe chronic uveitis with pupillary membrane formation. In these eyes aqueous formation is markedly reduced, owing to damage to the ciliary body. It is probable that in the postoperative period after cataract surgery a similar suppression of aqueous formation occurs in some patients with detachment of the ciliary body. We are attempting to obtain data to refute or substantiate this belief. We wish to thank Dr. Villaseca for his kind comments.

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HISTOPATHOLOGY OF THE STAR-FIGURE OF THE MACULAR AREA IN DIABETIC AND ANGIOSPASTIC RETINOPATHY

To the Editor:—In the article "Histopathology of the Star-Figure of the Macular Area in Diabetic and Angiospastic Retinopathy," published in the ARCHIVES in March, 1957, page 376, the authors, J. R. Wolter, R. I. Goldsmith, and R. L. Phillips affirm in the introductory paragraph, "a white star-figure in the macular area is a typical ophthalmoscopic finding in advanced chronic diabetic and angiospastic retinopathy."

It is my contention that this statement cannot be accepted on any terms, as it does not agree with facts and may at best lead to error. The macular star-fiure can be visualized in many conditions but never in diabetic retinopathy. The finding of a macular star-figure suggests renal retinopathy as the most likely diagnosis; it may suggest renal and diabetic retinopathy at most, but diabetic retinopathy in its pure forms (by far the most frequent) does not in its very typical ophthalmoscopic picture, during none of its periods, include the macular star-figure. It is therefore clear that one cannot refer to it as a typical ophthalmoscopic finding in advanced chronic diabetic retinopathy.

As regards angiospastic retinopathy, a designation first used by Gifford and Marquardt, in 1938, that has since become widespread, it is a slightly controversial maculopathy, the etiology of which is not well established. Under this name a series of conditions are grouped that show macular edema to various degrees, with or without pigmentation, with gray, white, or yellow exudative spots, changes in the perimacular vessels and preretinal vitreous, transient attacks of loss of vision or central blurring of vision, at times central scotoma, and always translucid scotoma plus metamorphoma in Amsler's girdle, changes in macular reflexes, and so forth. The macular star-figure is not usually mentioned in connection with angiospastic retinopathy, and, consequently, its inclusion as a typical finding in this ophthalmoscopic picture is unwarranted.

I have thought it in order to restate these concepts of elementary ophthalmoscopic semeiology. In Argentina, the macular star-figure is not considered as even an atypical finding in diabetic or angiospastic retinopathy. The literature on the subject shows this to be true of many other countries of both hemispheres.

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To the Editor:—In the discussed paper the term "macular star-figure" is used as a short designation for the groups of hard white spots which may form a more or less complete radiating figure around the fovea. Such groups of white spots

are often found in advanced cases of diabetic and angiospastic retinopathy. They are not an essential but a typical finding in the late stages of these conditions and were present in both cases discussed in the paper.

The term "angiospastic retinopathy" is not identical with that of "central angiospastic retinopathy" as used by Gifford and Marquardt for a disease which is also known as "chorioretinitis centralis serosa." Angiospastic retinopathy is another name for the condition also known as "arteriospastic, albuminuric, or nephritic retinitis." It was first used by Volhard, who found that the persistent arterial constriction represents the primary element of the retinal changes in this condition (comp. Elwyn, H.: Diseases of the Retina, New York and Toronto, The Blakiston Company, 1953, p. 67).

This is not the place to discuss whether the changes of advanced diabetic retinopathy constitute a characteristic entity or are caused in part by hypertension and arteriosclerosis. Our studies indicate that the white spots of the star-figure in the case with diabetic retinopathy (without hypertension) were of the same histological nature as those in the case of angiospastic retinopathy. However, in the case of diabetic retinopathy they seemed to be caused by primary hyalinization and partial obliteration of small blood vessels. The white spots in diabetic retinopathy are therefore considered to be a result of the characteristic vascular pathology of the retina in diabetes mellitus.

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News and Comment

ANNOUNCEMENTS

Oklahoma City Academy of Ophthalmology and Otolaryngology.—The Oklahoma City Academy of Ophthalmology and Otolaryngology will hold its fifth annual spring meeting on March 6 and 7, 1958. The meeting place is the main auditorium of the University of Oklahoma School of Medicine. The guest speakers are, in ophthalmology, Joseph A. Haas, M.D., Chicago, and in otolaryngology, Herman Semenov, M.D., Beverly Hills, Calif.

Further details can be obtained from E. N. Robertson Jr., M.D., 301 N. W. 12th St., Oklahoma City.

Correction

In the "Books" section of the Archives for October, 1957, Gregório Marañón was incorrectly listed as the author of "Ophthalmologica endocrina." Dr. Fermin Galindez Iglesias is the author of this book; Dr. Marañón wrote the introduction and the chapter on endocrine exophthalmos. The publisher is Espasa-Calpe, Spain and Argentina, and the price is 300 pesetas.

Obituaries

ARTHUR M. YUDKIN, M.D.

1892-1957

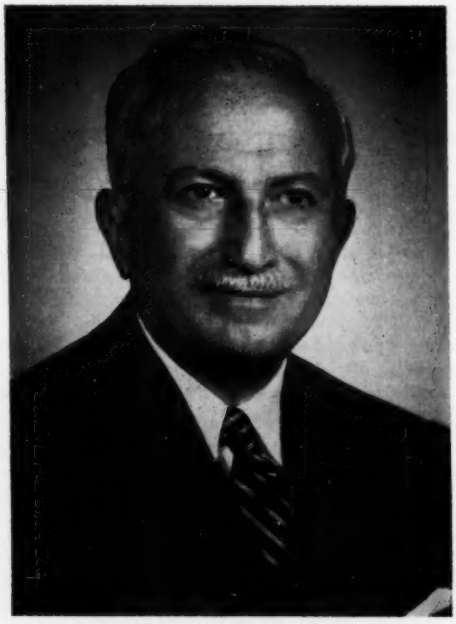
Dr. Arthur M. Yudkin, a clinical professor of ophthalmology at the Yale University School of Medicine, died of a heart attack May 2, 1957, while driving to his home in Woodbridge, Conn. He was buried on May 5, following memorial services in the Congregation Mishkan Israel on May 5.

Dr. Yudkin was returning to his home after attending a meeting of the Connecticut Medical Society in East Hartford. He collapsed after pulling his car off the Wilbur Cross Parkway in Wallingford and into the parking lot of a restaurant.

Dr. Yudkin is survived by his wife, the former Adele I. Weissman, of Woodbridge, whom he married in 1920, and two sons, Marvin Yudkin and Dr. Gerald Yudkin, of St. Paul. There are also three grandchildren.

Dr. Yudkin was born in Ansonia, Dec. 31, 1892, the son of Michael and Minnie Zandler Yudkin. He received his Ph.D. degree from the Yale Sheffield Scientific School in 1914 and his M.D. degree in 1917, also from Yale.

He was assistant resident physician at New Haven Hospital from 1917 to 1918 and an intern in ophthalmology in 1918. From that year to 1921 he was



Arthur M. Yudkin, M.D.
1892-1957

clinical assistant in ophthalmology and laryngology in the Yale School of Medicine, and for the next four years was clinical instructor in ophthalmology.

His promotions at the School of Medicine began in 1925, when he was made assistant clinical professor; in 1928 he became associate clinical professor, and in 1934 he was promoted to be clinical professor of ophthalmology, the position he held until his sudden death.

In addition to his large private practice, Dr. Yudkin was attending surgeon in ophthalmology at Grace-New Haven Hospital, attending ophthalmologist at the Hospital of St. Raphael, and consulting ophthalmologist at Griffin Hospital, Derby; Bristol Hospital, and to the National Society for the Prevention of Blindness.

In 1943 Dr. Yudkin was commissioned a major in the Medical Reserve Corps. He was a member of the American Academy of Ophthalmology and Otology, American Ophthalmological Society, National Society for the Prevention of Blindness, Society for Experimental Biology and Medicine, New York Academy of Medicine, Society of Clinical Ophthalmology, Sigma Xi honorary society, Milford Yacht Club, Race Brook Country Club, and Yale Faculty Club.

Dr. Yudkin was co-editor of "The Practitioners Library of Medicine and Surgery."

There is no more fitting expression of the feeling of his colleagues, patients, and friends than the eulogy of Rabbi Robert E. Goldburg, at the Mishkan Israel Temple, during the service held on May 5.

"No religion or philosophy ever taught can banish grief from the human heart, when the time comes which severs us from those we love. Those who feel deeply will grieve deeply. But although we cannot banish grief, yet it may be assuaged by gratitude and appreciation. We think of a person dear to us—someone we have loved and cherished, and though he may be dead—he is as near to us today as yesterday, as close to our hearts and minds as always. The influence of his personality, the attributes of his character, the tokens of his accomplishments and achievements never die. These enduring qualities are as infinite as man is finite. To them we turn for comfort and consolation, for strength and for inspiration.

"When we thus recall the life of Arthur Yudkin, we are confronted with an embarrassment of riches. A man of his gentle modesty would not appreciate a cataloguing of his virtues even at this sad hour. The newspapers have indicated his many contributions to his noble profession, and we need not rehearse them now. Yet we would be remiss to ourselves if we lost sight of the universal inspiration his life affords us. For Arthur was a dedicated man—a physician and healer, whose spiritual ancestors may be traced from the Bible and Talmud, to the great physician-philosopher Maimonidies, down to contemporary times. Achievement came not as a gift from heaven, but through devotion, effort, dedication to his fellow man, teaching others and un-ending study. The honor and respect with which he was held were not ends he sought, but rather the by-product of a life dedicated to human service. In Arthur there was quietness and dignity, gentleness and kindness, intelligence and resourcefulness. Nor can we discern any contradiction between the public man and the private one. For who knows better than his beloved wife and devoted sons the truly great and spiritual qualities that were his. He loved them dearly, as he did his daughters-in-law, grandchildren, and that pleasant and warm circle of family and friends which

surrounded him. These were his blessings—his solace and comfort which made possible his many labors. And now his life must be their solace and comfort, and the memory of it—their strength and inspiration. For though their heads are now bowed down in grief, their hearts should be lifted up in gratitude and appreciation for all the nobility in which they shared, and toward which they contributed. A great man in Israel was their husband, their father, their friend —a man who in serving and healing his fellow-men opened the eyes of more than he ever knew—the eyes of us all who stand in reverent tribute before the enduring memory of one of God's devoted servants among us. May we never fail to cherish that memory and may it ever bring us greater vision of our purpose on earth, and the inspiration to live our days as beautifully and lovingly as Arthur Yudkin lived his."

News and Comment

PERSONAL

Dr. Paul Boeder.—Dr. Paul Boeder, former Chief of the Bureau of Visual Science of the American Optical Company, has been appointed Associate Professor of Physiologic Optics in the Department of Ophthalmology at The State University of Iowa, Iowa City.

ANNOUNCEMENTS

Chicago Ophthalmological Society.—The Chicago Ophthalmological Society will hold its annual clinical conference on Feb. 21 and 22, 1958, at the Drake Hotel in Chicago.

The guest speakers will include Drs. Wendell L. Hughes, Hempstead, N. Y.; P. Robb McDonald, Philadelphia; Phillips Thygeson, San Jose, Calif.; Lorenz E. Zimmerman, Washington, D. C.; Eugene R. Folk, Chicago; Orville E. Gordon, Chicago; William F. Hughes, Chicago; Peter C. Kronfeld, Chicago; David Shoch, Chicago; Derrick Vail, Chicago, and Howard L. Wilder, Chicago.

The subjects will include a symposium on the complications of ophthalmic surgery, the zonule of the lens, glaucoma and retinal detachment surgery, plastic surgery techniques, management of glaucoma and cataract, melanotic tumors of the iris, and the structure of the vitreous.

Registration fee for the entire course, including round-table luncheons and buffet supper, is $45.00 and is payable to the registrar, Mrs. Edward J. Ryan, 1150 North Lorel Ave., Chicago 51.

The Fourteenth Annual Sanford R. Gifford Memorial Lecture will be delivered by Dr. Phillips Thygeson, of San Jose, Calif., on Friday, Feb. 21, 1958, at the Drake Hotel at 5:15 p.m. All ophthalmologists are invited to attend the Gifford Memorial Lecture and the buffet supper which follows.

Advanced Training of Research Scientists, P. H. S.—The Public Health Service has announced a new program of financial support for advanced training of research scientists in the field of neurological and sensory disorders.

The new program, designed to help research scientists obtain additional specialized training for careers in teaching or research, will be conducted by the National Institute of Neurological Diseases and Blindness, of the Service's National Institutes of Health, Bethesda, Md.

A previous program, under which about 75 scientists received advanced training during the last fiscal year, was concerned exclusively with clinical training. The new program is designed to encourage advanced training in either the clinical area or in such basic science areas as neurochemistry, neuropharmacology, neurophysiology, or neuroanatomy.

Individual awards under the program generally will be made for not less than nine months and for not more than one year. However, all awards are subject to renewal and may be continued for a period of three years. Stipends are determined individually in accordance with each applicant's qualifications and training needs. Such stipends may range from $5500 to $14,800 a year.

Application forms and instructions may be obtained by writing to the Chief, Extramural Programs Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Md. Completed applications should be submitted to the same address.

Applicants must be citizens of the United States or must have filed declarations of intent to become citizens. They must be free of any physical or mental disability that would interfere with the proposed training. In addition, they must have completed either (1) the residency training requirements in a clinical specialty,

or its equivalent, or (2) at least three years of pertinent postdoctoral training or research experience.

Special traineeships may be awarded for training at any institution in the United States or abroad qualified to give the particular training desired by the applicant.

The trainee may begin training at any time within ten months of the date of his award. During the period of training, the trainee will not be permitted to carry on the private practice of medicine; he may engage only in such teaching, clinical, and research activities as are a prescribed part of his training program.

The Treacher Collins Prize Essay.—Under this title, the Council of the Ophthalmogical Society of the United Kingdom has instituted a prize of £100, awarded triennially, for the best essay submitted upon a subject selected by the Council. The prize shall be open to qualified medical practitioners of any nationality. The essay shall be written in the English language.

The subject for the next award of the prize is "The Eye in Relation to the Collagen Diseases." The winning essay may be published in the *Transactions of the Ophthalmological Society,* if the Council so desire.

The closing date for sending in essays for this award is Dec. 31, 1959. Essays should be submitted to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 45 Lincoln's Inn Fields, London, W.C.2, from whom also any further particulars can be obtained. No name should be on any essay, but a distinguishing pseudonym or quotation, which should be upon a sealed envelope containing the candidate's name and address, should accompany the essay.

Refresher Course in Eye Surgery, University of Toronto.—The Faculty of Medicine of the University of Toronto will offer a Refresher Course in Eye Surgery from March 24 to 26, 1958. The guest surgeons will be Dr. Willis S. Knighton, New York, and Dr. P. Robb McDonald, Philadelphia.

The instruction will consist of operative clinics in the University teaching hospitals in the mornings and formal clinics, lectures, and case presentations in the afternoons. The staff of the department of ophthalmology will contribute to the course, which will be given to a minimum of 15 students, with a maximum registration of 40. A fee of $35.00 will be charged, payable to the Chief Accountant, University of Toronto. Applications should be made to the Dean of the Faculty of Medicine, not later than Jan. 31, 1958.

Annual Congress, Ophthalmological Society of the United Kingdom.—The Annual Congress of The Ophthalmological Society of the United Kingdom will be held in Cardiff, Wales, on April 17, 18, and 19, 1958.

The subject for discussion will be "Complications and Treatment of the Hypermature Cataract." This will be opened by Mr. G. T. Willoughby Cashell, Mr. C. A. Cook, and Mr. J. R. Hudson. Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress. It is emphasized that no member may speak for more than ten minutes.

There will also be a symposium on "The Role of the Toxoplasma in Ocular Disease," the speakers to include Prof. C. P. Beattie and Dr. J. K. A. Beverley.

The annual dinner will be held at the Park Hotel on Thursday, April 17. Members may bring guests.

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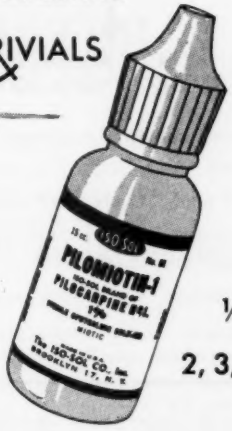

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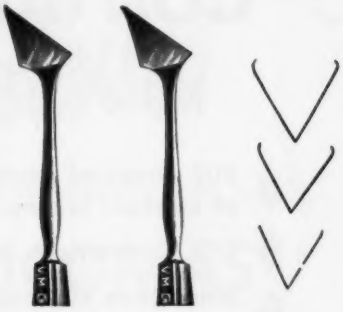

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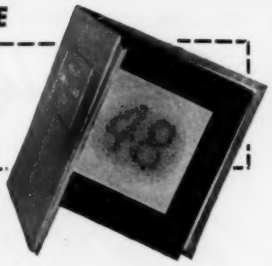

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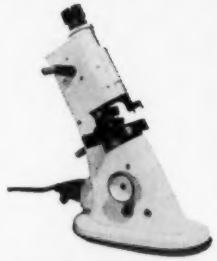

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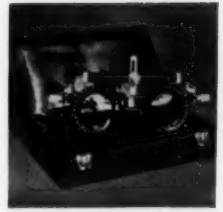

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"The Golden Link to Complete Service"

CASE HISTORY #3

Case History #3 explains the usefulness of Catarex Service in cases of bilateral cataract extractions. In this case, immediate vision was especially important, since the patient, a diabetic, lived alone and had to administer insulin to herself daily.

This case history emphasizes the fact that CATAREX T temporary cataract bifocals have proved themselves more versatile in aphakic cases *than any other form of temporary lens.* CATAREX T lenses are a simple answer to the old, complicated problem of easing the patient through the post-operative period. Why not use this splendid service on *your* next cataract case? Your optician or laboratory will be happy to supply details.

CASE HISTORY – Mrs. Y. Y.

A 67-year-old diabetic female had a left extracapsular lens extraction on October 26, 1954, and one week later, November 2, 1954, had a right intracapsular lens extraction. The post-operative course was normal. Patient was discharged November 10.

11-18-54: The patient was given the right and left +10.00 CATAREX T (temporary) lenses which had been ordered for her soon after discharge from the hospital. That she could avail herself of such a service was important, for she lived alone and had to administer insulin to herself daily.

11-23-54: Manifest O.D. +12.00Dsph. = 20/70—. Manifest O.S. +12.00Dsph. = 20/70+. Rx: these in CATAREX T (temporary style) straight-top bifocals. Until these were received by the patient, she continued to wear the previous lenses. This policy was followed in all subsequent changes, so the patient was never without a pair of CATAREX T bifocals.

12-16-54: Manifest O.D. +12.00 = 20/20—; Manifest O.S. +13.00 = 20/30. Rx: these in CATAREX T bifocals.

1-6-55: Manifest O.D. +12.00Dsph. ○ +1.00Dcyl. ax 165 = 20/15+; Manifest O.S. +11.00Dsph. ○ +1.00Dcyl. ax 90 = 20/20—. Rx: these in CATAREX T bifocals.

1-14-55: Manifest O.D. +13.50Dsph. ○ +1.00Dcyl. ax 165 = 20/15; Manifest O.S. +12.50Dsph. ○ +1.00Dcyl. ax 90 = 20/20+. Rx: these in CATAREX T bifocals.

4-21-55: Manifest O.D. +13.00Dsph. ○ +1.00Dcyl. ax 180 = 20/15+; Manifest O.S. +13.00 Dsph. ○ +1.00 Dcyl. ax 150 = 20/20. Rx: these in CATAREX T bifocals.

7-18-55: Manifest O.D. +13.25Dsph. ○ +1.00Dcyl. ax 180= 20/15+; Manifest O.S. +13.00Dsph. ○ +0.75Dcyl. ax 135 = 20/20+; +2.75D add = Jg. 0.75 @ 13″. Rx: these in permanent CATAREX D bifocals.

3-7-56: With permanent CATAREX D of 7-18-55, the right vision = 20/15+; the left vision = 20/20+.

The patient received her first pair of CATAREX T (temporary style) lenses eight days after discharge from hospital. She had six different pairs of temporary lenses during a period of eight months before the permanent CATAREX D bifocals were were prescribed. Because she had useful vision throughout this period, there was no urgency to prescribe the permanent lenses. The importance of this is indicated by the fact that there was no need to change these lenses eight months after they were prescribed. The patient was not only made visually comfortable post-operatively and enabled to administer insulin to herself daily, but was spared the expenditure of the relatively large amounts which she could ill-afford, for several changes of the regular post-cataract bifocals, which would have been mandatory if the Catarex Temporary Service were not available to her.

CATAREX 'T'
TEMPORARY CATARACT BIFOCAL LENSES BY **VISION-EASE**

Manufacturers of a complete line of quality multifocals

storz
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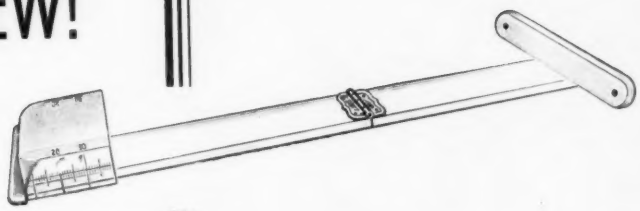
NEW!



Its length of 30 cm. permits a more nearly perpendicular position and makes deviation more evident.
Folding type lightweight plastic.

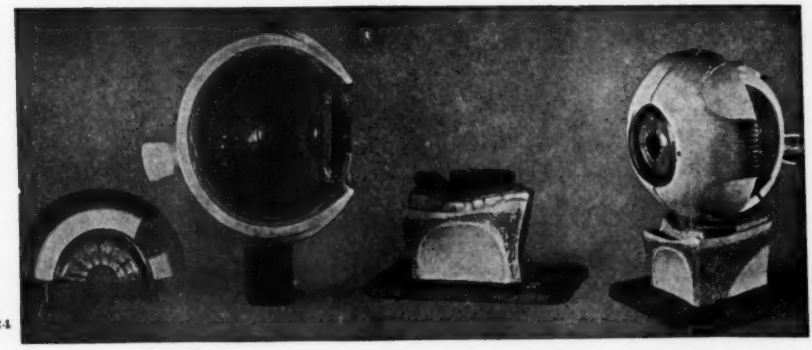
Journ. of Ophthal. Vol. 43, No. 1, Jan. 57

Exophthalmometer

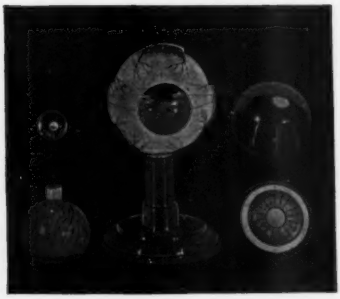
LESLIE C. DREWS, M.D., St. Louis, Missouri

E-5984 A new, simple, reliable model to permit comparison and even calibration of exophthalmometers. It can be sighted accurately at right angles, as its 50 mm. width provides excellent parallax. Has a simple second sighting device to facilitate holding parallel to the visual line.

Complete with case. **$20.00**



E-8124



E-8132

E-8124 MODEL EYE: enlarged 5 times, on base, mounted on bone, suitable for teaching purposes. **$56.50**

E-8132 MODEL EYE: enlarged 4 times, unbreakable, can be disassembled. **$27.50**

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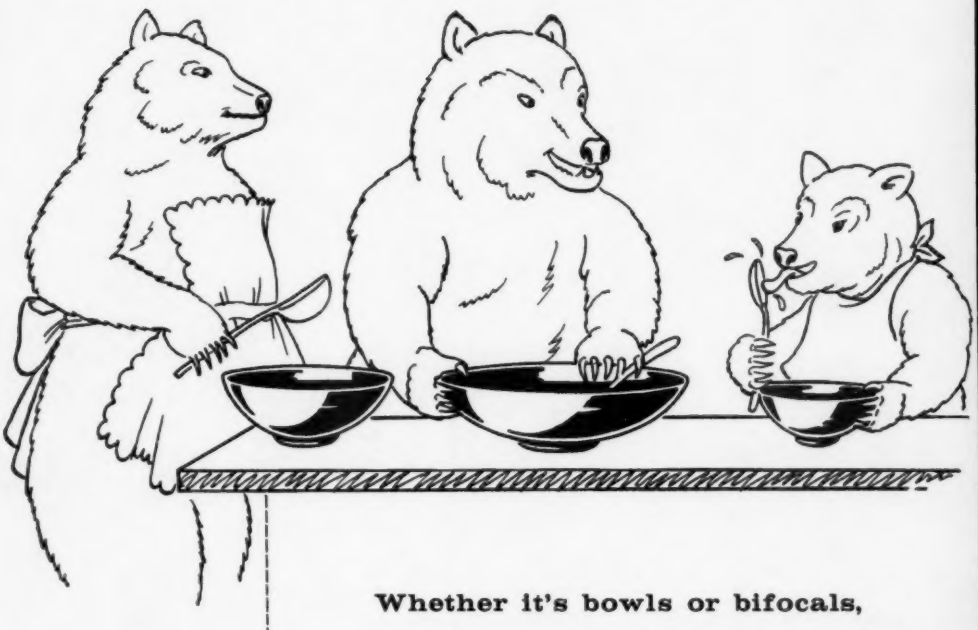
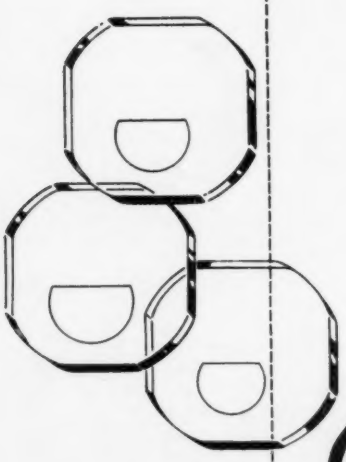


Whether it's bowls or bifocals,
need dictates size. You can't take care of man size near field requirements with a child size bifocal segment or vice versa.

The choice that Kurova F flat top fused bifocals give is a mighty helpful and convenient factor. The F is made three ways, with a 15 x 20 m/m, 16 x 22 m/m or a 17½ x 25 m/m near field. When you prescribe F's, it is a simple matter to pick the size called for by the case.

This three way segment selection added to Kurova F's sound scientific properties such as accuracy, freedom from color aberration and range of base curves and tints makes F's not only optically efficient but easy to use.



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